

**ADAS-cog plus the attention score:** This was initially the primary outcome measure but the sponsor changed it to a secondary measure after discussion with the division. The results of the comparison of the placebo and high dose group were similar with a statistically significant difference between groups at 12, 18 and 26 weeks and no difference between the low dose group and placebo.

**PDS:** The PDS was also a secondary outcome measure where the caregiver rated the activities of daily living. While the PDS score numerically favored the high dose group compared to the placebo group, the differences were associated with a p value of > 0.05 except in the LOCF analysis where the p value was 0.043.

Study 303: PDS: Mean change from baseline (higher score means greater improvement)				
	High dose (6 to 12 mg/day)	Low dose (1 to 4 mg/day)	Placebo	P value high vs placebo /low vs plb
<b>ITT</b>				
N	241	241	237	
Baseline	54.48	54.15	54.31	
Week 12	0.62	-1.14	0.06	0.60/0.26
Week 18	0.11	-1.78	-1.03	0.33/0.52
Week 26	0.05	-3.37	-2.18	0.066/0.326
<b>LOCF</b>				
N	198	225	223	
Baseline	53.31	54.29	54.79	
Week 12	0.47	-0.91	0.12	0.76/0.38
Week 18	0.09	-1.79	-0.98	0.415/0.522
Week 26	0.5	-3.31	-2.23	0.043/0.406

**MMSE:** The mean score for the high dose group improved by a mean of 0.2 points compared to baseline while the placebo group worsened 0.5 points. The differences were statistically significant for the ITT (p = 0.036) and LOCF (p = 0.02) data sets. The observed data set was not reported.

**GDS:** A comparison of the difference in the GDS score at week 26 of the high dose and placebo was statistically significant for the ITT and LOCF data sets. The observed cases was not reported.

**Subgroup analyses:** The sponsor reported that the subgroup analyses by sex, age at onset of disease (<65 years versus ≥ 65 years), baseline severity of disease (mild versus moderate), prior family history of disease, and intolerance or therapeutic failure with other anti-dementia drugs revealed no obvious trends in the characteristics of patients responding to treatment as defined by improvement in ADAS-Cog or CIBIC-Plus evaluations.

### Sponsor's conclusions:

The following significant differences were found at Week 26 (or early termination) between ENA-treated patients and placebo treated patients:

- improvement in the ADAS-Cog mean change from baseline in the 6-12 mg group versus worsening in the placebo group (ITT, LOCF, and OC).

- a greater percentage of 6-12 mg patients with a clinically significant improvement in the ADAS-Cog total score (ITT, LOCF, OC)
- a greater percentage of 6-12 mg and 1-4 mg patients rated improved on the CIBIC-Plus (ITT, LOCF, OC)
- improvement in the CIBIC-Plus mean rating of change from baseline in the 6-12 mg group (ITT, LOCF, OC)
- improvement in the ADAS-Cog with a mean change from baseline in the 6-12 mg group (ITT, LOCF and OC)
- a greater percentage of 6-12 mg patients with clinically significant improvement in the ADAS-Cog total score
- improvement in activities in daily living rated in the PDS in the 6-12 mg group versus worsening in the placebo group (LOCF only)
- a greater percentage of 6-12 mg patients with clinically significant improvement (ITT & LOCF)  
 Supportive evidence was obtained from the endpoint analysis of the MMSE and GDS. The MMSE mean change score was significantly different (showed improvement) in the 6-12 mg group compared with the placebo group (ITT & LOCF). The GDS mean score change from baseline showed significantly less worsening in the 6-12 mg group compared with the placebo group (ITT & LOCF).

Based on the predetermined criteria, these findings provide definitive evidence of the efficacy of ENA 6-12 mg in the treatment of patients with Alzheimer's disease.

**Reviewer's analysis:**

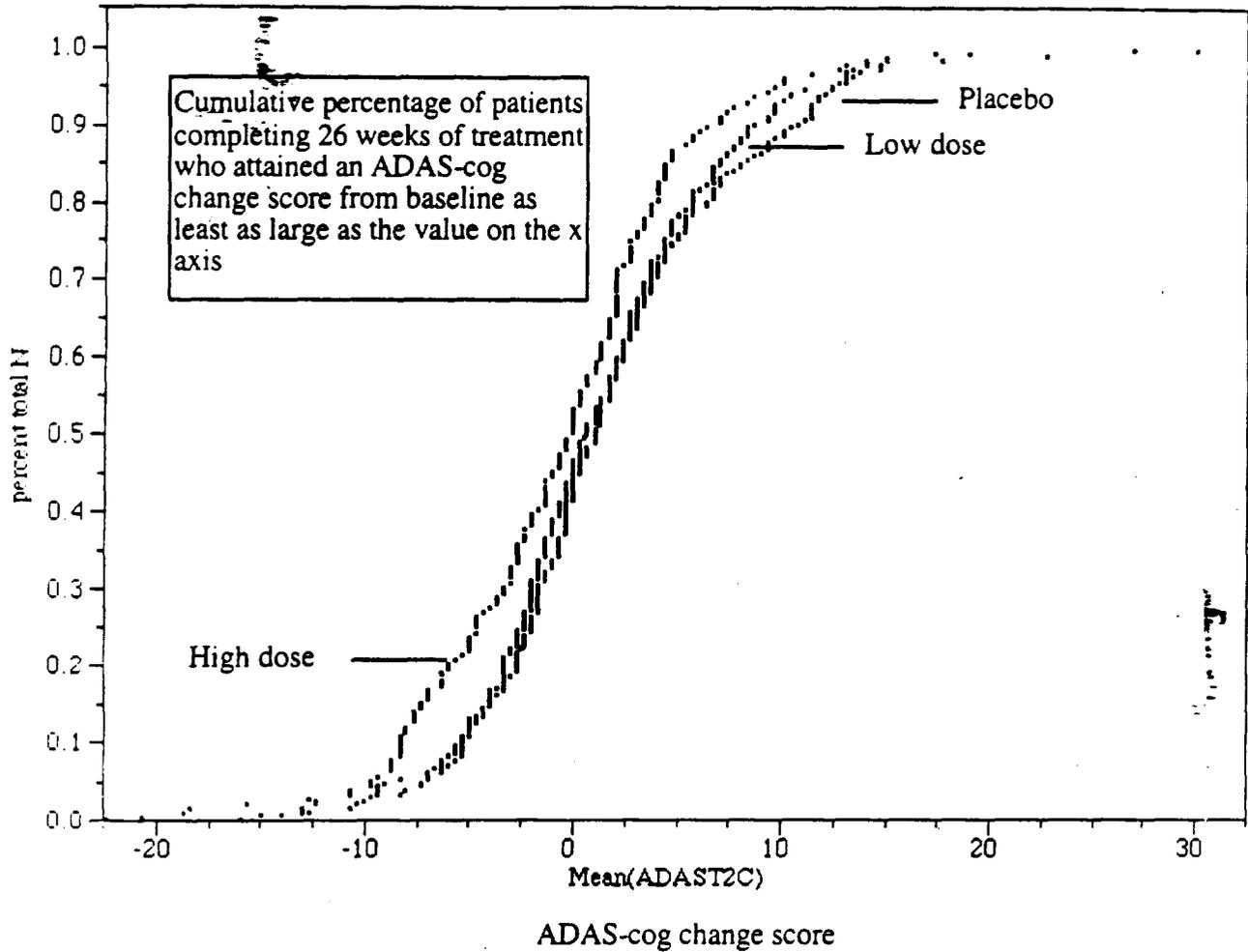
To conduct my analysis, I took all patient who were on drug for at least 60 days and had an assessment on study day  $\leq$  105 and included them in the 12 week analysis. For the week 18 analysis, I included patients who were on drug for at least 106 days and had an assessment between days 106 and 154. For the week 26 analysis, I included patients who had an assessment after day 154 and were on drug for  $>$  154 days. The results are summarized in the following table. P values were based on student t tests.

Study B303: ADAS-cog change from baseline for observed cases			
	Placebo	Low dose	High dose
Week 12 (N)	-0.13 (226)	-0.011 (228)	-1.59*# (209)
Week 18 (N)	1.42 (212)	0.42 (215)	-0.73*# (178)
Week 26 (N)	1.40 (210)	1.13 (209)	-0.54*# (161)

\*P value  $<$  0.05 in comparison with placebo  
 #p value  $<$  0.05 in comparison with low dose

By center: I compared the mean ADAS-cog change score for treatment group for each of the 47 centers for the week 26 observed cases. In 33 of the centers, the mean ADAS-cog change score was lower (better) in the high dose group compared to placebo. In 23 of the centers, mean ADAS-cog change score was lower (better) in the low dose group compared to placebo. There were 17 centers where the mean change for placebo patients score was  $\leq$  0. For the low dose, the mean change score was  $\leq$  0 in 13 centers and for the high dose, there were 27 centers where the mean changes score was  $\leq$  0.

By patient: I compared the cumulative percentage of patients with ADAS-cog change scores for each group. The results are summarized in the following figure.



by dose: Since there were few patients (< 16) taking doses of 6 or 9 mg/day by week 26, I took all patients in the high dose group and divided by the actual dose they were taking at the time of the assessment into two groups; those who were taking 12 mg/day and those who were taking < 12 mg/day.

Study B303: ADAS-cog change score for observed cases			
	Placebo	high dose <12 mg/day	High dose 12 mg/day
Week 12 (N)	-0.22 (227)	-0.85 (71)	-2.12* (123)
Week 18 (N)	1.41 (213)	-0.65* (62)	-0.81* (106)
Week 26 (N)	1.36 (202)	0.66 (55)	-1.52* (100)

\* P value < 0.05 in comparison with placebo

CIBIC plus: By the end of the study, the differences between the high dose group and placebo were associated with a p value of < 0.05. This was true for the intent to treat, LOCF and observed cases data sets. At week 12 and 18, only the difference between the high dose group and placebo were associated with p values > 0.05.

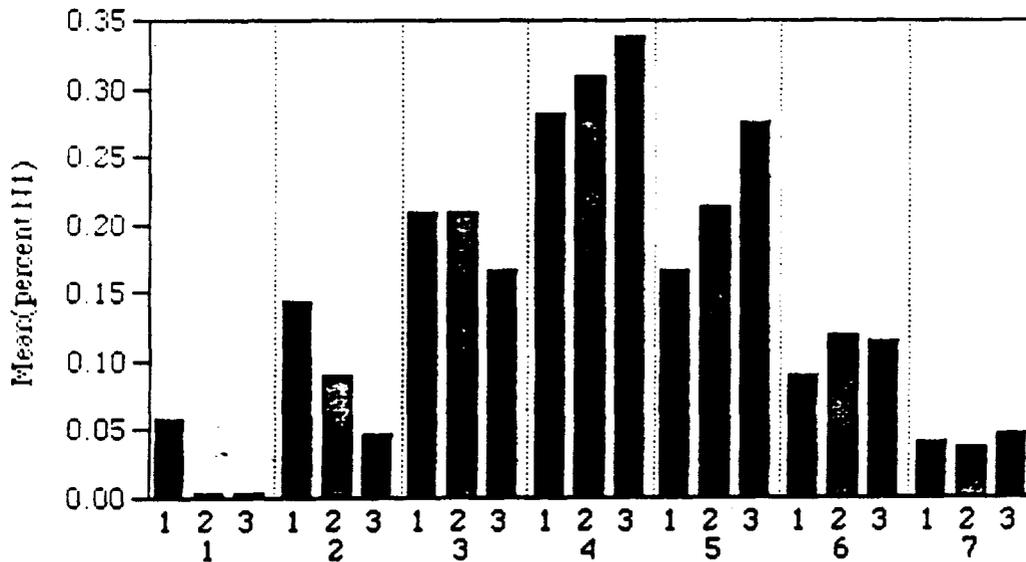
To conduct my analysis, I took all patient who were on drug for at least 60 days and had an assessment on study day  $\leq 105$  and included them in the 12 week analysis. For the week 18 analysis, I included patients who were on drug for at least 106 days and had an assessment between days 106 and 154. For the week 26 analysis, I included patients who had an assessment after day 154 and were on drug for  $> 154$  days. The results are summarized in the following table. P values were based on student t test for comparison of each pair.

Study B303: CIBIC plus for observed cases			
	Placebo	Low dose	High dose
Week 12 (N)	4.1 (223)	4.0 (224)	3.9 (201)
Week 18 (N)	4.2 (213)	4.1 (213)	3.8*# (173)
Week 26 (N)	4.4 (209)	4.2 (207)	3.8*# (166)

\*P value  $< 0.05$  in comparison with placebo  
 #p value  $< 0.05$  in comparison with low dose

By center: I compared the CIBIC plus scores for 43 centers for the week 26 observed cases. In 27 of 43 centers, the high dose group had better scores than placebo group. In 23 centers, the low dose group scored better than the placebo group. In 8 centers, the placebo group scored better than either the high dose or low dose group.

By patient: I took the percentage of patients in the week 26 observed cases data set with each CIBIC plus score for each group and summarized the information in the following figure:



A comparison of CIBIC scores (1 to 7) for each treatment group with 1=high dose, 2= low dose and 3= placebo

By component: I took the week 26 observed cases data set and compared the results for the cognitive, functional and behavioral sections of the CIBIC plus. The results are summarized in the following table:

Study B303 comparison of the CIBIC plus components			
	Placebo (N=209)	Low dose (N=207)	High dose (N=166)
Cognitive	4.35	4.09*	3.84*#
Functional	4.27	4.29	4.04*#
Behavioral	4.05	4.00	3.85

\*P value < 0.05 in comparison with placebo  
#p value < 0.05 in comparison with low dose

by dose: I took all patients in the high dose group and divided by the actual dose they were taking at the time of the assessment into two groups; those who were taking 12 mg/day and those who were taking < 12 mg/day.

Study B303: CIBIC plus score for observed cases			
	Placebo	high dose <12 mg/day	High dose 12 mg/day
Week 26 (N)	4.36 (195)	3.85* (59)	3.74* (95)

\*P value < 0.05 in comparison with placebo

Responders: I arbitrarily defined a responder as a patients who improved on both the ADAS-cog and CIBIC plus and as patients who did not worsen on either the ADAS-cog and CIBIC plus.

Study B303: %responders = no change or better on ADAS-cog and CIBIC plus			
	Placebo	Low dose	High dose
Week 12 (N)	38% (213)	40% (225)	54%* (213)
Week 18 (N)	30% (211)	38% (214)	47%* (172)
Week 26 (N)	32% (212)	31% (206)	42%* (160)

\*P value < 0.05 in comparison with placebo  
#p value < 0.05 in comparison with low dose

Responders = improvement on ADAS-cog and CIBIC plus			
	Placebo	Low dose	High dose
Week 12 (N)	15% (213)	18% (225)	27%* (213)
Week 18 (N)	13% (211)	14% (214)	26%* (172)
Week 26 (N)	14% (212)	16% (206)	28%* (160)

\*P value < 0.05 in comparison with placebo

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By dose: I analyzed the ADAS-cog and CIBIC plus by dose for the week 26 observed cases.  
Study 303: Week 26 observed cases for CIBIC plus

Level	Number	Mean	Std Dev	Std Err Mean
0.0	209	4.37799	1.18309	0.08184
0.5	1	5.00000	.	.
1.0	2	4.50000	0.70711	0.50000
2.0	9	4.77778	1.39443	0.46481
2.5	4	4.25000	0.50000	0.25000
3.0	6	4.33333	1.03280	0.42164
4.0	175	4.13714	1.31898	0.09971
4.5	1	4.00000	.	.
6.0	15	3.66667	1.49603	0.38627
7.0	7	3.42857	1.98806	0.75142
8.0	8	4.12500	1.35620	0.47949
9.0	11	3.81818	1.32802	0.40041
10.5	13	3.53846	1.50640	0.41780
12.0	100	3.71000	1.43756	0.14376

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## Study 304

This study was completed after submission of the NDA. The final study report has not been submitted. Results of the study were provided in data sets.

### Protocol:

**Design:** This was a 26 weeks, randomized, placebo controlled, double blind, parallel study. Patients were randomized equally to one of three groups. In one group, patients were titrated the maximally tolerated dose between 2 and 12 mg/day given as a bid dose (1 to 6 mg bid with food in the morning and evening). In the second group, patients were titrated to a dose ranging between 2 to 12 mg/day given as a tid dose (3 to 6 mg bid with food). The third group received placebo.

The dose titration phase lasted up to 12 weeks. The initial dose was 2 mg/day. This was increased to 3 mg/day on day 4. The dose could be increased at weekly intervals thereafter until the maximally tolerated dose was reached (between 2 and 12 mg/day). To improve tolerability, antiemetics were allowed. By the end of week 12, all patients were on their highest tolerated dose in their dose range. If the patients could not tolerate 2 mg/day, they were discontinued from the study.

During the maintenance phase, dose increase or decrease within the assigned range was allowed based on tolerance with the aim to achieve the maximum dose. The investigator was allowed to stop the dose for up to 3 doses in a week except 24 hours prior to a safety visit and 72 hours before an efficacy assessment.

**Doses:** Capsules of 0, 0.5, 1, 1.5, 3, 4.5 and 6 mg were used. Doses were given in the morning and evening for the bid dosing and morning, noon and evening for tid dosing. All doses were given with food. The bid doses consisted of two even doses while for the tid doses, at some dose levels, higher doses were given at noon and in the evening.

**Sample:** 600 patients were to be enrolled at 30 to 40 centers with at least 6 per treatment group per center.

**Selection:** Patients, age 50 to 85, with probable AD by the NINCDS criteria with scores of 10 to 26 on the MMSE were enrolled. The patients were otherwise generally healthy. Patients requiring skilled nursing care were excluded. Patients with a total score of  $\geq 5$  on the modified Hachinski ischemia scale were excluded.

**Terminate:** Drop outs were to be retrieved.

**Medication:** Psychoactive medication was prohibited except for occasional use of chloral hydrate (doses up to 2 grams), low dose of haldol (0.5 to 3 mg/day) and short acting benzodiazepines (temazepam up to 20 mg/day). There was a one month washout for patients on cholinergic agents.

**Outcome:** Primary ADAS-cog, CIBIC plus. Initially, the protocol called for adding the ADAS-noncog attention score to the ADAS-cog.

**Analysis:** An interim analysis may be performed with a stopping alpha of 0.0001 and a final alpha of 0.05. Amendment 10 called for an unblinded interim analysis when 50%

of patients completed week 26 and almost all patients have been enrolled. The safety data will be combined with the other studies. There was no planned interim analysis of the efficacy data. There was an independent safety monitoring board.

The primary outcome was the change from baseline for the week 26 ADAS-cog and the week 26 CIBIC plus score. Data sets include the LOCF, ITT, retrieved drop outs and observed cases as defined in the DNDP imputation schemes. Assessments from day 1 to 105 were assigned to analysis week 12. Assessments from day 106 to 154 were assigned to analysis week 18 and assessments done after day 155 were to be assigned to week 26. The primary analysis will be the comparison of the high dose with placebo. If this is significant, then pairwise comparisons will be performed for the other comparisons. ANCOVA will be used to analyze the ADAS-cog with baseline as a covariate. The CIBIC plus will be analyzed using ANOVA.

Proportion of patients showing improvement (An improvement in the ADAS-cog is a change score of  $\geq 4$  points and in the CIBIC plus, it is a score of 1, 2 or 3.

Subgroup analyses will be patients who had elevated LFTs on tacrine or were intolerant to other anti dementia drugs, severity of AD at baseline, early onset of AD, therapeutic failures on tacrine, sex, race, exceptional responders ( $> 7$  point change on the ADAS-cog or a rating of 1 or 2 on the CIBIC plus)

When scale items are missing, the total will be calculated number by taking the mean of the items present and multiplying by the number of items for the complete scale. If more than half of the items are absent, no value will be assigned.

Amendments: Amendment 7 (5/3/95) separated the worksheets of the CIBIC plus so that the rater would not have continuous access to notes from previous assessments. Amendment 11 called for using the 11 point ADAS-cog scale.

## Results:

**Disposition:** The planned sample size was 600. For the interim analysis, 346 patients were randomized by the cut off date of 10/31/95. 295 (85%) completed the 26 weeks of treatment. 13, 13 and 19% withdrew from the placebo, tid and bid groups, respectively. 5, 8 and 12% of the patients withdrew for adverse events from the placebo, tid and bid groups, respectively.

From the final data set, 678 patients were enrolled with 227, 229 and 222 in the tid, bid and placebo groups, respectively.

**Baseline characteristics:** From the interim data, the demographics and baseline characteristics of the treatment groups were similar. The mean age was 70 to 71 years old with a range from 52 to 89. 53 to 60% of the patients were female and 97 to 99% were white. The mean duration of the dementia was approximately 43 months with 40% rated as mild and 58% rated as moderate according to the NINCDS criteria. 1 to 5% of patients took cholinesterase inhibitors. The previous medication use was similar between groups. During the study approximately 30% of patients on active treatment took GI medications compared to 16% in the placebo group.

**Dosage:** From the final data sets, 22 and 26 of the patients in the tid and bid dosage groups took more than 12 mg/day. Of the remaining patients, the mean maximum dose was approximately 10 mg/day and the mean dose was approximately 8 mg/day.

**Sponsor's conclusions:**

The sponsor did not submit a study report for this study.

**Reviewer's analysis:**

ADAS-cog: By the endpoint of the study, there was a statistically significant difference in favor of the drug in comparison of placebo and the bid dose group. The differences were associated with p values < 0.05 at 12, 18 and 26 weeks. The treatment difference between the bid group and placebo was about 2.7 points after 26 weeks. For the observed cases data set, the mean ADAS-cog change from baseline was improved for the bid dose group and worsened for the placebo group. The differences between the bid and tid dose groups were numerically in favor of the bid dose group but the differences were not associated with p values < 0.05. In the comparison of the placebo and tid dose group, statistically significant differences were noted at weeks 12 and 18 but not week 26. The results are summarized in the following table.

The results are summarized in the following table. P values were based on student t tests.

Study B304: ADAS-cog change from baseline for observed cases			
	Placebo	tid dose	bid dose
Week 12 (N)	0.81 (206)	-0.91* (197)	-1.70* (206)
Week 18 (N)	1.35 (191)	-0.58* (182)	-1.77* (196)
Week 26 (N)	2.00 (184)	0.60 (174)	-0.73* (180)

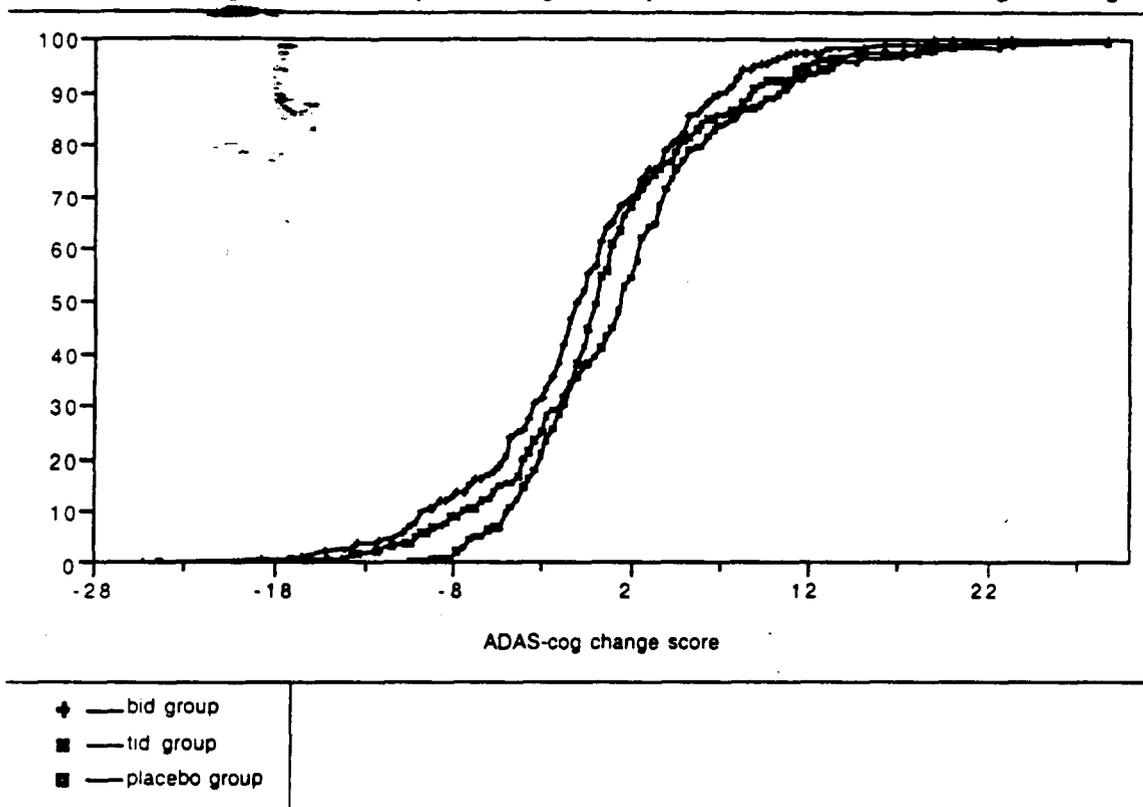
\*P value < 0.05 in comparison with placebo

By center: I compared the mean ADAS-cog change score for treatment group for each of the 37 centers for the week 26 observed cases. In 33 of the centers, the mean ADAS-cog change score was lower (better) in the bid dose group compared to placebo. In 25 of the centers, mean ADAS-cog change score was lower (better) in the tid dose group compared to placebo. There were 9 centers where the mean change for placebo patients score was  $\leq 0$ . For the tid dose, the mean change score was  $\leq 0$  in 12 centers and for the bid dose, there were 21 centers where the mean changes score was  $\leq 0$ .

By patient: I compared the cumulative percentage of patients with ADAS-cog change scores for each group. The results are summarized in the following figure.

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**Study 304: Cumulative percentage of patients with ADAS-cog change score**



by dose: I grouped the actual dose by week 26 into  $\leq 9$  mg/day and  $> 9$  mg/day.

Study B304: ADAS-cog change from baseline for week 26 observed cases			
	Placebo	tid dose	bid dose
$> 9$ mg/day (N)	2.05 (183)	-0.10* (86)	-1.22* (103)
$\leq 9$ mg/day (N)	2.05 (183)	0.98 (87)	-0.18* (73)

\*P value  $< 0.05$  in comparison with placebo

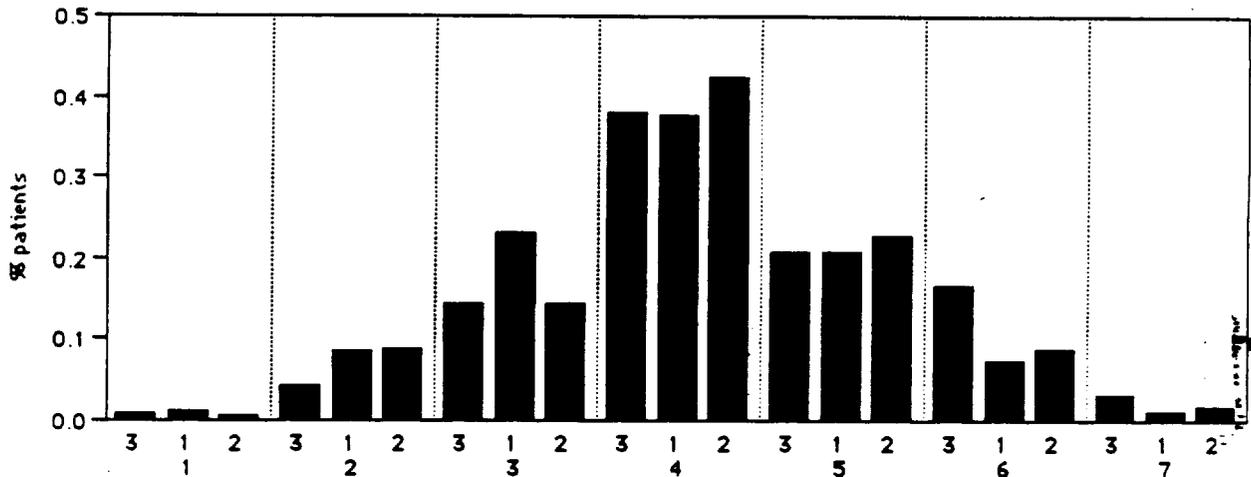
CIBIC plus: At weeks 12, 18 and 26, the differences between the bid dose group and placebo were associated with a p value of  $< 0.05$ . This was also true for differences between the tid dose group and placebo at weeks 12 and 18. At week 26 the difference between the tid group and placebo was associated with a p value  $> 0.05$ . The results are in the following table.

Study B304: CIBIC plus for observed cases			
	Placebo	tid dose	bid dose
Week 12 (N)	4.27 (199)	3.88* (189)	3.91* (200)
Week 18 (N)	4.33 (187)	4.04* (182)	3.91* (194)
Week 26 (N)	4.38 (179)	4.12 (167)	3.95* (177)

\*P value  $< 0.05$  in comparison with placebo

By center: I compared the CIBIC plus scores for 37 centers for the week 26 observed cases. In 19 of 43 centers, the bid group had better scores than placebo group. In 21 centers, the tid group scored better than the placebo group. In 8 center, the placebo group scored better than both the bid dose and. tid dose group.

By patient: I took the percentage of patients in the week 26 observed cases data set with each CIBIC plus score for each group and summarized the information in the following figure. Group 1= bid group, 2+ tid group and 3 = placebo. The CIBIC scores go from 1= improvement to 7 = worsening.



By component: I took the week 26 observed cases data set and compared the results for the cognitive, functional and behavioral sections of the CIBIC plus. The results are summarized in the following table:

Study B304 comparison of the CIBIC plus components			
	Placebo (N=179)	bid dose (N=177)	tid dose (N=167)
Cognitive	4.23	3.98*	4.18
Functional	4.38	4.02*	4.18*
Behavioral	4.01	3.97	3.90

\*P value < 0.05 in comparison with placebo

By dose: I grouped the actual dose by week 26 into ≤ 9 mg/day and > 9 mg/day.

Study B304: CIBIC plus for week 26 observed cases				
	Placebo	tid dose	bid dose	overall
> 9 mg/day (N)	4.38 (177)	3.93* (81)	3.84* (103)	3.88* (184)
≤ 9 mg/day (N)	4.38 (177)	4.30 (86)	4.11 (76)	4.21 (162)

\*P value < 0.05 in comparison with placebo

Responders: I arbitrarily defined a responder as a patients who improved on both the ADAS-cog and CIBIC plus and as patients who did not worsen on either the ADAS-cog and CIBIC plus.

Study B304: %responders = no change or better on ADAS-cog and CIBIC plus			
	Placebo	tid dose	bid dose
Week 12 (N)	42 (202)	46 (192)	51 (204)
Week 18 (N)	34 (188)	41 (181)	53 (195)
Week 26 (N)	30 (178)	37 (165)	46 (171)

Study B304: %responders = no change or better on ADAS-cog and CIBIC plus				
	Placebo	tid dose	bid dose	overall
> 9 mg/day (N)	30 (178)	37 (83)	50 (102)	45 (185)
≤ 9 mg/day (N)	30 (178)	37 (82)	38 (69)	37 (151)

Study B304 %responders = improvement on ADAS-cog and CIBIC plus			
	Placebo	tid dose	bid dose
Week 12 (N)	9% (202)	21% (192)	24% (204)
Week 18 (N)	12% (188)	17% (181)	24% (195)
Week 26 (N)	12% (178)	15% (165)	23% (171)

By dose: I analyzed the ADAS-cog and CIBIC plus by the dose the patients was on at week 26.

Study 304 Week 26 observed cases ADAS-cog change from baseline by dose				
Level	Number	Mean	Std Dev	Std Err Mean
0.0	177	1.93032	5.76504	0.4333
1.5	1	1.00000	.	.
2.0	1	4.00000	.	.
3.0	7	1.09524	3.18396	1.2034
4.0	14	-1.16667	7.51835	2.0094
5.0	24	-0.13889	5.44354	1.1112
6.0	17	2.76471	4.55637	1.1051
7.0	27	0.09877	4.05182	0.7798
8.0	32	-0.28125	6.86171	1.2130
9.0	28	1.91666	7.91343	1.4955
10.5	28	-0.85715	5.43228	1.0266
12.0	157	-0.63694	7.03536	0.5615

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Study 304: CIBIC plus week 26 observed cases				
Level	Number	Mean	Std Dev	Std Err Mean
0.0	177	4.38418	1.21981	0.09169
1.5	1	5.00000	•	•
2.0	1	4.00000	•	•
3.0	7	4.57143	1.27242	0.48093
4.0	14	4.35714	0.84190	0.22501
5.0	24	4.04167	0.99909	0.20394
6.0	17	4.23529	1.25147	0.30353
7.0	27	4.11111	1.21950	0.23469
8.0	32	4.12500	1.00803	0.17820
9.0	28	4.25000	1.17458	0.22197
10.5	28	3.85714	1.11270	0.21028
12.0	157	3.89172	1.17440	0.09373

rl

Randy Levin, M.D.  
rl/Novmeber 30, 1997

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11/30/97

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DATE: January 22, 1998

FROM: Judith A. Racoosin, MD, MPH  
Division of Neuropharmacological Drug Products  
HFD-120

TO: File: NDA 20-823

SUBJECT: Nested Case-Control Study of Mortality with Exelon (rivastigmine)

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### Introduction

During the initial review of mortality in the Exelon NDA, Dr. Armando Oliva identified that the mortality rate in the Exelon-treated group exceeded that in the placebo-treated group in the phase 2/3 trials by six-fold. Dr. Oliva's estimate of the person-time exposure to Exelon of 1546 person-years (over all dose ranges) was based on the data in text table 3 5.1 of the ISS, "Cumulative Duration of Exposure: ENA 713 Mean Daily Dose, All Therapeutic Studies". Using this estimate, the mortality rate for Exelon treated patients was 30 per 1000 person-years ( $46/1546 \times 1000$ ). In comparison, the mortality rate in placebo patients based on the sponsor's estimate of 434 person-years placebo exposure was 5 per 1000 person-years.

Because the estimate of person-time exposure to Exelon was based on summary data, I used the "DAR" data files for studies 303, 351, and 352 provided by the sponsor to calculate a more exact person-time estimate. Using these estimates and the deaths occurring in these studies, the mortality rate in the Exelon-treated group was 10.1 deaths per 1000 person-years ( $6/592.3$ ) vs. 0 deaths per 1000 person-years ( $0/286.1$ ) for the placebo-treated patients. Furthermore, in studies 303 and 352, the two studies utilizing a high-dose range up to 12 mg, there were 3 deaths in the high dose group and none in the low-dose or placebo groups. These suggestions of excess mortality in the Exelon-treated group led us to examine the mortality data further. Capitalizing on the titration design of randomized controlled trials and extensions, we aimed to determine whether there was a dose-response relationship between Exelon dose and death.

### Methods

#### *Study Cohort*

Our study utilized a data file provided by the sponsor submitted September 18, 1997. This data file contained the following information for all patients exposed to Exelon during the randomized controlled trials (RCT) and/or extension (EXT) trials: demographic data, identification numbers of RCT and EXT trials with the corresponding number of days the patient was in each portion; whether the patient died during a trial, and if so, the number of days between the patient's last medication dose and their death. Thirty-one deaths were included in this file. Two deaths occurred during phase 2 trials. Since we did not have daily dosing information for all phase 2 patients in the data files provided by the sponsor we excluded all phase 2 patients from the analysis.

### *Case Definition*

We defined a case in our study as a death occurring in a phase 3 trial within 30 days of the last dose of medication. Five phase 3 deaths occurred greater than 30 days after the last dose of medication and were thus excluded from the analysis. Therefore our study included 24 cases.

### *Control Selection*

For each case, the time to death was determined by calculating the number of observation days between initiation of the RCT and the day of death. The number of observation days was the sum of the number of days in the RCT, the number of days in the EXT (if applicable), and the number of days between the last dose and the death date (by definition, between 0 and 30). For all the other patients, observation days was the sum of the number of days in the RCT, the number of days in the EXT (if applicable), and 30 additional days of observation (to balance for the 30 potential days to death for the cases). All cases and potential controls were sorted by number of observation days to determine which patients could serve as controls for the cases when being matched on failure time (see figure 1).

Once a risk set was determined for each case based on observation days, potential controls were identified that matched the case on study number and origin of patient (domestic vs. foreign). Among the patients that matched the case, five controls were randomly selected. This same process was utilized for each case. Cases occurring later in time could function as controls for cases occurring earlier in time.

### *Covariate Collection -*

For each case and control patient dosage data was extracted from the DAR data files provided by the sponsor. For studies 304, 305, 353, and 355, the DAR files from the 120 day safety update were used since they contained more complete data on the patients in those trials. The following dosage variables were determined: highest prescribed dose (HPD), highest actual dose (HAD), last prescribed dose (LPD), last actual dose (LAD), days since last dose change (DSLDC), cumulative actual dose (CAD), cumulative prescribed dose (CPD), difference between cumulative actual dose and cumulative

prescribed dose (DIFF), cumulative dose at the last prescribed dose (CDLPD), cumulative dose at the last actual dose (CDLAD). Variables pertaining to HPD, LPD, and CAD were also calculated based on the patient's baseline weight (in kg) resulting in the variables HPD/kg, LPD/kg, and CAD/kg. The above variables were examined as continuous and categorical variables. Four categories were determined for each variable based on quartile distribution with the exception of HPD, HAD, LPD, and LAD. For the latter variables the categories were defined based on the approximate range of treatments in the RCTs. LPD, LPD/kg, HPD, and HPD/kg were also tested as continuous variables.

### *Analysis*

\_\_\_\_\_ was used to perform conditional logistic regression to analyze the risk sets (a "matched analysis").

To rule out the possibility of the results being dependent on sampling, the analysis was repeated using a different set of 5 randomly selected controls for each case. For this analysis only the variables LPD and LPD/kg were collected.

### **Results**

Table 1 summarizes the odds ratios by category for the variables LPDcat and LPDkgcat. The elevated risk of death associated with higher doses observed for these two variables with the first set of 120 controls are confirmed by the second set. When LPD and LPDkg were tested as continuous variables, the trend of elevated risk of death with higher Exelon doses was corroborated (p-values 0.063 and 0.005, respectively). The relationship between each of these variables and mortality was not confounded by age, gender, or baseline weight.

Both cases and controls were taking the last prescribed dose for a median of 50 days. There was no relationship between the number of days since last dose change and mortality. A trend towards elevated risk of mortality with increasing quartile of HPDkgcat (the categorical variable for HPD/kg) was also observed, but not for HPDcat or HADcat.

Variables related to cumulative exposure to Exelon (CPD, CAD, DIFF, CPDLLD, CADLLD) showed no consistent relationship with mortality.

### **Discussion**

This nested case control study of mortality in the Exelon NDA suggests that mortality is related to the patient's last prescribed dose, with patients receiving the highest doses having a ten-fold higher risk of mortality as compared with patients receiving the lowest

doses. A dose-response relationship for mortality was still observed after controlling for baseline weight.

The confirmation of the dose-response relationship between Exelon dose and mortality with a second set of controls makes it unlikely that the result was due to sampling. One limitation of our study is the small number of controls matched to each patient. The small number of controls reduced the precision of the estimates.

Because patients were not randomized to final dose, it is possible that patients who were more likely to die received higher doses. However, without knowing a patient's comorbidities during their drug exposure (e.g. concurrent cardiovascular conditions, exposure to certain medications, drug-related weight loss), this explanation can not be proved or disproved.

At this point we will ask the sponsor to investigate this safety signal more thoroughly. There are additional deaths in the phase 3 studies which were not included in the data file from the sponsor which need to be included in any further study of mortality. Furthermore, the sponsor needs to evaluate covariates which may modify the relationship between Exelon dose and death, such as pre-existing cardiovascular disease, the use of cardiac medications, or substantial weight loss during drug treatment.

*ISI*  
\_\_\_\_\_  
Judith A. Racoosin, MD, MPH

cc: NDA 20-823  
Leber/Levin (electronic copy)/Burkhart/Oliva/Racoosin

*1/22/97  
Agree that appears to be an  
association between ↑ dose  
& death. It needs a  
more in-depth evaluation  
by the sponsor  
ISI*

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Figure 1. Sampling Procedure for Nested Case Control Study of Exelon Mortality

Patient 1	-----D (84)
Patient 2	-----C (28)
Patient 3	-----C (56)
Patient 4	-----C (112)
Patient 5	-----C (21)
Patient 6	-----D (126)
Patient 7	-----C(70)
Patient 8	-----D (14)
Patient 9	-----C (42)
Patient 10	-----C (98)

C= censored; D= death; (#)= days of observation

Risk Set 1: Case - patient #8  
Potential controls - patients #1,2,3,4,5,6,7,9,10

Risk Set 2: Case - patient #1  
Potential controls - patients #4,6,10

Risk Set 3: Case - patient #6  
Potential controls - none available

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Table 1. ODDS RATIOS FOR NESTED CASE CONTROL STUDY OF EXELON MORTALITY  
 (LPD= last prescribed dose, LPDkg= last prescribed dose per kg)

dose	LPDcat			quartiles	LPDkgcat		
	control set #1 (n=120) OR (95% CI)	control set #2 (n=120) OR (95% CI)	combined (n=240) OR (95% CI)		control set #1 (n=120) OR (95% CI)	control set #2 (n=120) OR (95% CI)	combined (n=240) OR (95% CI)
<4mg	1	1	1	1	1	1	1
4-6 mg	6.6 (0.7 - 62)	4.1 (0.5 - 36)	5.5 (0.6 - 49)	2	2 (0.3 - 13)	1.4 (0.3 - 7)	1.4 (0.3 - 7.2)
6.1-9 mg	5.4 (0.4-70)	5.5 (0.5 - 36)	5.3 (0.5 - 60)	3	3.9 (0.6 - 25)	2.9 (0.6 - 13)	3.5 (0.7 - 17)
>9 mg	11.5 (1.0 - 128.1)	8.1 (0.8-78)	9.8 (0.99 - 97)	4	6.0 (0.9 - 40)	4.8 (1.0 - 24)	4.7 (0.95 - 23)

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## Review and Evaluation of Clinical Data

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<b>NDA (Serial Number)</b>	<b>20-823</b>
<b>Sponsor:</b>	<b>Novartis</b>
<b>Drug:</b>	<b>Exelon</b>
<b>Proposed Indication:</b>	<b>Dementia of Alzheimer's type</b>
<b>Material Submitted:</b>	<b>Safety Team Memorandum</b>
<b>Correspondence Date:</b>	<b>1/22/98</b>
<b>Date Received / Agency:</b>	<b>1/22/98</b>
<b>Date Review Completed</b>	<b>1/23/98</b>

---

### 1. Introduction

During my initial review of the Exelon NDA, I identified that the mortality rate (expressed in person years of exposures) in placebo controlled trials (RCT's) was higher, by 4 to 6 fold, in the Exelon treated patients compared to those on placebo (30 vs. 5-7 per 1,000 patient-yrs, respectively). Based on this finding, the safety team, and Dr. Judy Racoosin in particular, undertook a more in-depth analysis of the mortality data. In particular, she performed a nested case-control study of the mortality data. I review the findings of Dr. Racoosin's study in this document.

### 2. Nested Case-Contol Mortality Study

#### 2.1 Methods

I briefly describe Dr. Racoosin's methods, here, however I refer the reader to her memorandum dated 1/22/98 for more detail. She calculated more accurate patient exposure data from datasets which the sponsor had submitted in the NDA and in a subsequent dataset which the safety team had requested. She analyzed data from patients in the controlled trials as well as the open-label extensions. Since accurate exposure data from phase 2 subjects were lacking, these were excluded from the study (2 deaths).

She defined a case in the study as a death occurring in a phase 3 trial within 30 days of the last dose of medication. Five phase 3 deaths occurred greater than 30 days after the last dose of medication; therefore, the study contained 24 cases.

Observation days were calculated by determining the number of days from the start of the controlled trial until death occurred. This was the sum of observation days in the RCT plus the number of observation days in the extension plus the number of days between the last dose and the death date (the latter term by definition was between 0-30). All cases and potential controls were sorted by observation days to determine which patients could serve as controls.

Potential controls for a case were patients who had observation days equal or greater than the case. These patients defined a "risk set." Five controls for each case were randomly selected from these risk sets, matched on study number, and origin (domestic vs. foreign).

The following variables were defined or calculated: highest prescribed dose (HPD), highest actual dose taken (HAD), last prescribed dose (LPD), last actual dose (LAD), days since last dose change (DSLDCCH), cumulative actual dose (CAD), cumulative prescribed dose (CPD), difference between cumulative actual dose and prescribed dose (DIFF), cumulative dose at the last actual dose (CDLAD). The variables HPD, LPD, CAD were also normalized by body weight, giving rise to HPD/kg, LPD/kg, and CAD/kg.

## 2.2 Analysis

The identified variables were analyzed as both continuous and categorical values. Four categories were defined based on approximate treatment ranges, <4mg, 4-6mg, >6-9mg, >9mg).

was used to perform a conditional logistic regression to analyze the risk sets (a "matched analysis").

To exclude sampling bias, the analysis was repeated using a different set of 5 randomly selected controls for each case. For the second analysis, only LPD and LPD/kg were collected.

## 2.3 Results

The results of the analysis are shown in Dr. Racoosin's memo, Table 1. It shows that patients on high dose Exelon as their last prescribe dose (>9-12mg) had an approximate 10 fold risk of dying compared to patients last exposed to <4mg. Ninety-five percent confidence intervals (95% CI) were quite broad and did not reach statistical significance. Patients last treated with mid-range doses (4-9mg) showed intermediate risk, suggesting a dose-response phenomenon. Similar findings were observed with normalized doses based on body weight (the odds ratios were approximately 5 for the high dose group).

## 3. Comments

1. This is a significant safety signal, suggesting that patients treated with the high dose Exelon have a substantially increased risk of death compared to those on lower doses.
2. The analysis is limited in that it includes only 24 cases, which is the maximum number permitted into the study based on the available data. In the 120 Day safety update, the sponsor reports a total of 55 deaths as of 3/31/97. They should also have accurate exposure data for these deaths.
3. I concur with Dr. Racoosin that the sponsor should investigate this safety signal more thoroughly using information from the additional deaths. The issue will likely delay action on this NDA.



**f a c s i m i l e**  
**T R A N S M I T T A L**

To: Robert Kowalski, Pharm. D.  
Sponsor: Novartis  
Fax #: 973-781-6325  
Re: NDA 20-823; Exelon Capsules  
Date: January 23, 1998  
Pages: 7 (including cover letter)

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Dear Mr. Kowalski:

During the review of mortality in the Exelon NDA the review team has identified what appears to be an association between Exelon dose and mortality. The Division would like to discuss this relationship and its potential impact on the NDA application. Dr. Leber has requested that I provide you with Dr. Racoosin's review to assist your team in preparing for the upcoming meeting. A telecon has been set up for January 30, 1998 at 2:30 pm.



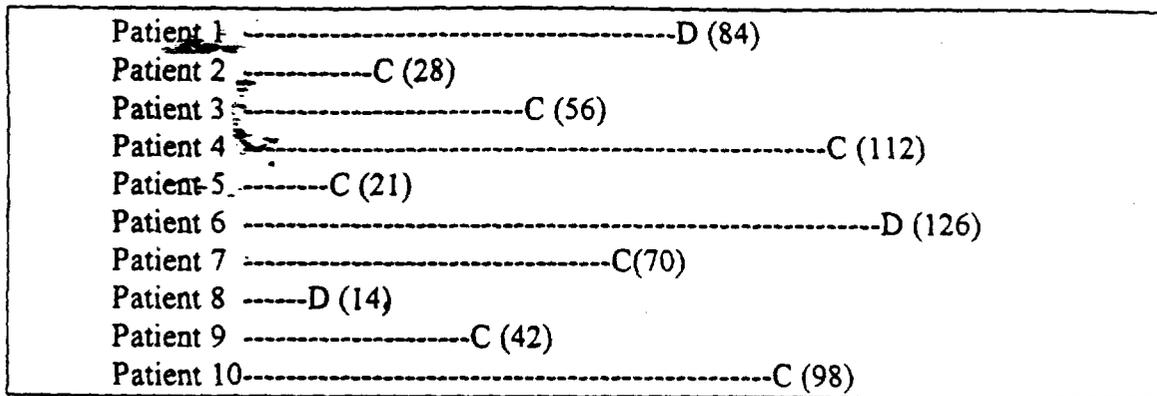
From the desk of...

Melina Malandrucchio, R.Ph.  
Project Manager  
Division of Neuropharmacological Drug Products /  
HFD-120  
Food and Drug Administration  
Rockville, Maryland 20857

301-594-5526  
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JSJ 1/23/98

Figure 1. Sampling Procedure for Nested Case Control Study of Exelon Mortality



C= censored; D= death; (#)= days of observation

Risk Set 1: Case - patient #8  
Potential controls - patients #1,2,3,4,5,6,7,9,10

Risk Set 2: Case - patient #1  
Potential controls - patients #4,6,10

Risk Set 3: Case - patient #6  
Potential controls - none available

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**Table 1. ODDS RATIOS FOR NESTED CASE CONTROL STUDY OF EXELON MORTALITY**

(LPD= last prescribed dose, LPDkg= last prescribed dose per kg)

dose	LPDcat			quartiles	LPDkgcat		
	control set #1 (n=120) OR (95% CI)	control set #2 (n=120) OR (95% CI)	combined (n=240) OR (95% CI)		control set #1 (n=120) OR (95% CI)	control set #2 (n=120) OR (95% CI)	combined (n=240) OR (95% CI)
<4mg	1	1	1	1	1	1	1
4-6 mg	6.6 (0.7 - 62)	4.1 (0.5 - 36)	5.5 (0.6 - 49)	2	2 (0.3 - 13)	1.4 (0.3 - 7)	1.4 (0.3 - 7.2)
6.1-9 mg	5.4 (0.4-70)	5.5 (0.5 - 36)	5.3 (0.5 - 60)	3	3.9 (0.6 - 25)	2.9 (0.6 - 13)	3.5 (0.7 - 17)
>9 mg	11.5 (1.0 - 128.1)	8.1 (0.8-78)	9.8 (0.99 - 97)	4	6.0 (0.9 - 40)	4.8 (1.0 - 24)	4.7 (0.95 - 23)

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Printed by Robrin Nighswander  
**Electronic Mail Message**

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 06-Feb-1998 07:50am  
**From:** Greg Burkhart  
BURKHARTG  
**Dept:** HFD-120 WOC2 4034  
**Tel No:** 301-594-5536 FAX 301-594-2859

**TO:** See Below  
**Subject:** Exelon Mortality: Discussion with Novartis on 2/5/98

February 6, 1998

We had a TC with Novartis's group working on the Exelon mortality issue. Ravi led the discussion from their end. Judy and I represented the division with Armando & Randy present for the first part of discussion. I also called Ravi back after Judy had checked some of their concerns regarding our analysis.

The main points:

1) Patients exposed to placebo in the RCTs were allowed in the matching.

We clarified that only patients with placebo and then exelon exposure in the extension could be in the study. Novartis removed these patients from the RCT matches and it decreased the ORs. We pointed out that these patients were also serving as controls (and cases) in the extension and were likely to have less exposure there because of their placebo experience. Thus, if anything, they have to be removed from the cohort. Judy, redid our analysis with these patients removed and it made no difference in the results. It is also OK with us if they add in all the placebo experience and the 1 placebo death.

2) We did not use the correct number of days for patients who dropped out, presumably went off drug, then waited to enter extension.

We were not aware that there were such patients in the cohort. According to Ravi, this happened a lot "about 20 to 30% of the time". We agreed that the principal was to define the total number of days of observation. If a patient dropped out of the RCT, waited, irrespective of whether they stayed on or went off drug, we should have used this time. Judy checked the data file and found that there was only 1 control in one risk set and 2 controls in the other risk set where this occurred. Thus, while the concern was theoretically an issue, it did not bias our findings.

3) The magnitude of the ORs by category of dose is dependent on cut scores.

We checked this and they are correct. However, the high dose group still had an increased OR of at least 3 and this concern has nothing to do with the analysis that used dose as a continuous measure. The cutoff score issue is reflecting the size of the sample not a bias.

4) Poisson regression results are negative.

This was the most interesting point. Our nested case control analysis is

supposed to be an unbiased estimate of the relative difference in mortality rates by dose. If their Poisson regression (I think they mean a person-time analysis) was negative that would be compelling.

It turns out when I spoke to Ravi again that they had used our samples not the full cohort. Of course our samples are conditional on the time of case occurrence supposedly representing the cohort person-time at each death time. That is not the same as having a random sample of the cohort's experience (i.e., case/cohort study). Thus, I suggested that to verify our nested case-control findings, they could simply assign each patient day to a dose group for the full cohort that we used to sample from (we didn't do this because it is difficult to program). In fact, this is the simplest way for them to verify our findings. (I should have thought of it earlier.)

5) Future plan.

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col to

**Distribution:**

TO: Robbin Nighswander	( NIGHSWANDER )
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CC: Armando Oliva	( OLIVAA )
CC: Randy Levin	( LEVINR )
CC: Judith Racoosin	( RACOOSINJ )
CC: John Feeney	( FEENEYJ )

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## Statistical Review and Evaluation

NDA#: 20-823

FEB 18 1998

Name of Applicant: **Novartis Pharmaceuticals Corporation**Name of Drug: **Exelon**Documents Reviewed: Vols. 1.243, 1.244, 1.248, 1.249, 1.251, 1.252, 1.253, 1.257, 1.313,  
1.314Medical Officer: **Randy Levin, M.D., HFD-120**Background

The sponsor has submitted the results of four (4) multicenter, placebo controlled, double-blind trials as evidence of the efficacy of Exelon in Alzheimer's disease. Trials 303 and 352 were 26 week titration studies with two prespecified titration ranges. Trial 351 compared 3 fixed doses of Exelon to placebo. Trial 304 has been reviewed by the medical officer, Dr. Levin. He has determined that the results of that study support the efficacy of Exelon, and thus is not reviewed in this document.

All tables are taken from the NDA

Trial 352

Evaluations of the ADAS-Cog and CIBIC-plus were made at baseline and at weeks 12, 18, and 26. Patients were titrated within ranges: 1-4 mg, 6-12 mg or placebo for the first 12 weeks of the trial (titration phase). The next 14 weeks was the maintenance phase. As per original protocol (10/24/94), the ADS-Cog was analyzed with and without the "Attention" item. For the ADAS-Cog, the primary analysis was an Analysis of Covariance on the change from baseline using the baseline value as the covariate at week 26. ANOVA was to have been used if the test for homogeneity of treatment slopes was significant at the 10% level or the pooled slope was not different from zero at the 10% level. For the CIBIC-plus, the primary analysis was the two-way analysis of variance. However, a later document called Statistical Appendix (6/24/96) describes a categorical data analysis on the CIBIC-plus by dichotomizing the 7 point scale into improvement (scores 1,2,3) and no change (score 4) or worsening (scores 5,6,7). Categorical analyses were done with both CMH and logistic regression. The latter was used to control for various baseline covariates

The sample size of 200 subjects/group was determined by requiring 90% power to detect a mean difference of 3 points on the ADAS-Cog with a standard deviation of 9.0.

The protocol does not specify which of the possible data sets (ITT, LOCF, OC, etc) would be regarded as primary.

The ITT value at 26 weeks was the last value for a patient on or off treatment. According to the sponsor, therefore, there were no artificial "zero" changes from baseline, i.e. baseline - baseline=0.

To control error associated with multiple comparisons, a closed testing procedure was used whereby a test was first conducted on the high dose group against placebo at .05, and then on the low dose group against placebo only if the high dose comparison was significant.

## Results

The trial randomized 699 patients among 22 centers: 6-12 mg: 231, 1-4 mg: 233, and placebo: 235. Treatment arms were well-balanced in numbers and each center accrued approximately 30 patients. Table 1 displays various aspects of patient disposition as the trial progressed. Note that

- 1) The LOCF efficacy sample consists of 616 patients. By definition, these are patients who received at least one dose of study medication and had at least one post-baseline assessment.
- 2) There were significantly more dropouts to adverse events in the 6-12 mg group than placebo. Many of these were GI complaints. This raises the issue of blinding as patients were titrated upwards in the 6-12 mg group during the first 12 weeks of the study.
- 3) Of the 154 who dropped out, 61 returned for an efficacy assessment at week 26 (Retrieved Dropouts)

Table 2 indicated that the treatment arms were well-balanced with respect to Demographic background variables. The same was true for potential prognostic factors.

Table 3a displays the results for the ADAS-Cog for the ITT, LOCF, and OC data sets, respectively, while Table 3b displays summary p-values with details from the linear model for all the data sets. Evidently, the assumptions for the ANCOVA were not met (note 2 at the base of Table 3a), so that the analyses were done by ANOVA. The results are clearly significant for both dose groups in all 4 meaningful data sets (the Retrieved Drop Out-RDO having too few patients). In 26 weeks placebo patients worsened approximately 4 points while patients in the high dose group essentially stayed the same as a baseline. The performance of the low-dose group was intermediate. There is a 14 patient discrepancy between the number of completers listed in Table 1 (545) and the sum of the treatment numbers in the OC table in Table 3 (531). Whatever the explanation of the discrepancy, it would have no substantial effect on the results.

The sponsor also determined that approximately 20% of the high dose patients improved four (4) or more points whereas approximately 7% of the placebo patients did.

Table 4 displays the CIBIC-plus results using the protocol-specified ANOVA. Between 20-25% of the high dose patients improved from baseline while approximately 15% of the placebo patients did.

Table 5 displays the results of *pairwise* CMH analyses (stratified by investigator) of the CIBIC-plus. Note that the CMH test was not the protocol-specified analysis, but was contained in the "Statistical Appendix" mentioned earlier, along with the planned ANOVA. The high dose group did not achieve statistical significance in the ITT sample.

### Trial 303

This trial was identical in design to Study 352.

### Results

The trial randomized 725 patients among 44 centers in Canada, Austria, Switzerland, Germany, and France: 6-12 mg: 243, 1-4 mg: 243, and placebo: 239. Treatment arms were well-balanced in numbers and enrollment ranged from 5 to 36 patients/center. Table 6 displays various aspects of patient disposition as the trial progressed. By protocol, centers with less than 6 patients in at least one treatment arm were combined within the respective country.

1) The LOCF efficacy sample consists of 660 patients. By definition, these are patients who received at least one dose of study medication and had at least one post-baseline assessment.

2) As in Study 352, there were significantly more dropouts to adverse events in the 6-12 mg group than placebo. Many of these were GI complaints. This raises the issue of blinding as patients were titrated upwards in the 6-12 mg group during the first 12 weeks of the study.

3) Of the 134 who dropped out, 72 returned for an efficacy assessment at week 26 (Retrieved Dropouts).

Table 7 indicated that the treatment arms were well-balanced with respect to Demographic background variables. The same was true for potential prognostic factors.

Table 8a displays the results for the ADAS-Cog for the ITT, LOCF, and OC data sets, respectively, while Table 8b displays summary p-values with details from the linear model for all the data sets. In 26 weeks, placebo patients worsened approximately 1.3 points while patients in the high dose group essentially tended to be the same as at baseline or improve slightly.

In the LOCF and OC data sets, the results are sensitive to the grouping of the centers as was called for in the protocol. Within each country, all centers with at least one treatment arm with less than 6 patients would be pooled.

If centers are not grouped in the LOCF data set, the p-value for the comparison of high dose to placebo is .056, rather than .001. This results exclusively from a drastic shift in the lsmeans change from baseline in the high dose group. Instead of a treatment difference of approximately 2.25 using the grouping, the treatment difference declines to approximately 1.35 without grouping.

If centers are not grouped in the OC data set, the p-value for the comparison of high dose to placebo is .25, rather than .001. Again, this results exclusively from a drastic shift in the lsmeans change from baseline in the high dose group. Instead of a treatment difference of approximately 2.25 using the grouping, the treatment difference declines to approximately 1.0 without grouping.

The sponsor also determined that approximately 25% of the high dose patients improved four (4) or more points whereas approximately 17% of the placebo patients did.

The results of this trial are different from those of study 352 in two respects:

- 1) In study 352, the placebo worsened approximately 4 points (mean) from baseline, considerably more than in study 303, and
- 2) Unlike in study 352, the low dose group did not come close to statistical significance in study 303

Table 9 displays the CIBIC-plus results using the protocol-specified ANOVA. Unlike in Study 352, the 1-4 mg group did not reach statistical significance.

The pairwise CMH analyses (Table 10) (stratified by center) of the CIBIC-plus indicate statistically significant improvement for both doses compared to placebo. About 40% of the high dose patients improved from baseline while approximately 20% of the placebo patients did.

#### Reviewer's Comments

In order to explain the difference between the pooled and unpooled analyses, this reviewer found the following: There were 13 of the 43 (useful) centers in which the placebo did better than the high dose drug arm. All of these centers were "small" in that they were pooled with other centers. By including the treatment by center interaction term in the ANCOVA *without grouping*, either small treatment differences or reversals in "small" centers have the same weight as treatment differences in other centers ("unweighted analysis"). (The protocol did not state whether or not the interaction term would be in the model. However, the sponsor reported results only using the interaction term in the N.A.) This phenomenon probably outweighs the influence of pooling marginal results into fewer pooled groups and then doing an unweighted analysis.

It is true that by not pooling, one preserves some gross imbalances between the numbers among the Treatment X Center cells. The calculated treatment difference can then be a complicated, and often difficult to interpret, function of the data. A more balanced design results from pooling and yields more straightforward calculations of the treatment difference. On the other hand, there is presumably no reason to suspect that true treatment effects vary considerably from center to center. Thus, the unweighted analysis should give essentially the same answer as the pooled analysis.

Ultimately, probably the most important question is whether or not there is a systematic relationship between the size of the center and the unknown treatment effect. One could at least say that the results of the ADAS-Cog are somewhat dependent on how the data is analyzed. However, one may be encouraged by the fact that if pooling is not done, and the interaction term is not in the model, then results are very similar to those when pooling is done and interaction is in the model (sponsor's analysis). **This means that when each center is allowed to contribute to the analysis on its own, weighted by its individual sample sizes, the result is statistically significant to the same degree as the sponsor's analysis.**

### Trial 351

This trial compared 3 fixed doses (3 mg, 6 mg, <sup>9</sup>9 mg) of Exelon to placebo. Patients were titrated up to their assigned fixed dose in the first 12 weeks. The protocol called for 150 patients/group to have 90% power for detecting a mean difference of 3.5 points on the ADAS-Cog using a standard deviation of 9. Otherwise the statistical analysis plan was the same as that of the other two trials.

### Results

The trial randomized 702 patients among 14 centers in the US : 3 mg: 175, 6 mg: 176, 9 mg: 178 and placebo: 173. Treatment arms were well-balanced in numbers and enrollment ranged from 5 to 36 patients/center. **Table 11** displays various aspects of patient disposition as the trial progressed. By protocol, centers with less than 6 patients in at least one treatment arm were combined within the respective country.

- 1) The LOCF efficacy sample consists of 591 patients. By definition, these are patients who received at least one dose of study medication and had at least one post-baseline assessment.
- 2) As in Studies 352 303, there were significantly more dropouts to adverse events in the high dose (9 mg) group than placebo. Many of these were GI complaints.
- 3) Of the 240 who dropped out, 58 returned for an efficacy assessment at week 26 (Retrieved Dropouts)

Table 12 indicated that the treatment arms were well-balanced with respect to Demographic background variables. The same was true for potential prognostic factors.

Table 13a displays the results for the ADAS-Cog for the ITT, LOCF, and OC data sets, respectively, while Table 13b displays summary p-values with details from the linear model for all the data sets. In 26 weeks, placebo patients worsened approximately 2.5 points while patients in the 6 mg and 9 mg groups worsened average of at most 1 point. The performance of the 3 mg group was somewhat but not statistically better than placebo in all three sample data sets.

The sponsor also determined that the active dose groups had higher proportions of patients who improved four (4) or more points than placebo, but statistical significance was not consistent over the sample data sets.

Table 14 displays the CIBIC-plus results using the protocol-specified ANOVA. No dose group reached statistical significance over placebo in any data set. The results were much weaker using the CMH analysis (Table 15).

#### Reviewer's Comments and Conclusion

The sponsor has submitted two trials (352 and 303) which demonstrate statistically significant differences between the high (flexible) dose and placebo with respect to changes from baseline on the ADAS-Cog and the CIBIC-plus. These results are robust to various methods of analysis including longitudinal analyses (mixed effects linear models) applied to the OC sample. It should be noted that even though various analyses on the CIBIC-plus are positive in both trials, *the median score was 4 (no change) for both the high dose group and the placebo group.*

In the fixed dose (after 12 weeks titration) trial (351), both the 9 mg and 6 mg groups reached statistical significance over placebo on the ADAS-Cog but not on the CIBIC-plus ( $p=0.084$  for the mean CIBIC-plus in the LOCF sample was the lowest p-value of any analysis).

ISI  
David Hoberman, Ph.D.  
Mathematical Statistician

Concur: Dr. Sahlroot

Dr. Chi  
11/18/78  
ISI/ISI

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cc.

N. A. # 20-823

HFD-120/Dr. ~~Leber~~

HFD-120/Dr. Katz

HFD-120/Dr. Levin

HFD-120/Mr. Purvis

HFD-120/Mr. Nighswander

HFD-344/Dr. Barton

HFD-710/Dr. Chi

HFD-710/Dr. Sahlroot

HFD-710/Dr. Hoberman

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## Patient Disposition: By Treatment

Variable	6-12mg	1-4mg	PBO
Randomized N	231	233	235
Completed n Pct	149 (65)	199 (85)	197 (84)
Discontinued n Pct	82 (35)	34 (15)	38 (16)
Reason for Disc: Adverse Experiences	57 (29)	19 (8)	17 (7)
--Adverse Events	66 (29)	19 (8)	17 (7)
--ECG Abnormalities	1 (<1)	0	0
Death	1 (<1)	0	0
Withdr. of Consent	9 (4)	10 (4)	10 (4)
Protocol Violation	0	0	1 (<1)
Treatment Failure	0	0	4 (2)
Failure Return Visits	2 (1)	1 (<1)	0
Other	3 (1)	4 (2)	6 (3)

Variable	6-12mg vs PBO	1-4mg vs PBO
Randomized N		
Completed n Pct		
Discontinued n Pct	<0.001 *	0.701
Reason for Disc: Adverse Experiences	<0.001 *	0.732
--Adverse Events	<0.001 *	0.732
--ECG Abnormalities	0.496	
Death	0.496	
Withdr. of Consent	1.000	1.000
Protocol Violation	1.000	1.000
Treatment Failure	0.123	0.123
Failure Return Visits	0.245	0.498
Other	0.504	0.751

500 patients screened

Percentages based on number of patients randomized within each treatment group

Statistical comparisons based on Fisher's Exact Test. \* p < 0.05

## Population Summary: By Treatment

Population Grouping	6-12mg	1-4mg	PBO	Total
	N	N	N	N
Randomized (Intent-to-Treat)	231	233	235	699
Patients receiving study medication	230	232	235	697
Safety - Patients with at least one on drug safety evaluation	230	232	235	697
Last Observation Carried Forward - Efficacy	181	217	216	616
Screened Dropouts at Week 26 - Efficacy	33	11	17	61

Patients randomized but not receiving study medication-

6-12mg: 1  
1-4mg: 1  
PBO: 2

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TABLE 2

## Demographic and Background Information: By Treatment

Variable	6-12mg N = 231	1-4mg N = 233	PBO N = 235	P-values
Age (years)				
N	231	233	235	0.216 *
Mean	73.8	74.9	74.8	
Std	7.60	7.24	7.45	
Median	74.0	76.0	75.0	
Min				
Max				
Age (%)				
<=65	35 (15)	23 (10)	25 (11)	
66-75	95 (41)	89 (38)	93 (40)	
76-85	87 (38)	112 (48)	106 (45)	
>85	14 (6)	9 (4)	11 (5)	
Sex (%)				
Male	75 (32)	100 (43)	98 (42)	0.041 * **
Female	156 (68)	133 (57)	137 (58)	
Height (cm)				
N	230	233	235	0.166 *
Mean	163.3	165.1	164.0	
Std	10.37	10.53	10.75	
Median	163.0	165.0	163.0	
Min	130	137	135	
Max	193	193	193	
Weight (kg)				
N	225	232	231	0.218 *
Mean	66.1	68.2	66.4	
Std	14.47	14.32	13.29	
Median	64.0	67.0	66.0	
Min	37	39	39	
Max	130	122	115	
Race (%)				
Caucasian	225 (97)	221 (95)	222 (94)	0.201 **
Black	6 (3)	9 (4)	10 (4)	
Asian/Oriental	0 (0)	0 (0)	2 (1)	
Other	0 (0)	3 (1)	1 (<1)	
Dementia Dur (Months)				
N	231	233	235	0.670 *
Mean	38.4	39.3	40.4	
Std	22.15	24.55	27.73	
Median	36.0	36.0	36.0	
Min	5	3	6	
Max	126	138	180	

\* Based on one-way analysis of variance

\*\* Based on Chi-square test

Std=Standard Deviation Min=Minimum Max=Maximum

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**ADAS-Cog: Change from Baseline Score  
Summary Statistics in the ITT Population**

Visit	Statistic	6-12	1-4	PBO	6-12 vs PBO	1-4 vs PBO
Week 12	N	231	233	234		
	Baseline Mean	22.61	22.23	22.12		
	Mean Change	0.56	-1.45	-2.06	0.000*	0.200
Week 18	N	231	233	234		
	Baseline Mean	22.61	22.23	22.12		
	Mean Change	-0.18	-1.80	-3.35	0.000*	0.002*
Week 26	N	231	233	234		
	Baseline Mean	22.61	22.23	22.12		
	Mean Change	-0.31	-2.36	-4.09	0.000*	0.002*

- Higher change scores indicate greater improvement.
- Baseline adjusted change indicated by (adj). Where adjusted changes not given, ANCOVA assumptions not met.
- \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANCOVA/ANOVA (SAS Type III analysis).
- Details of the analysis are found in the appendices.

**ADAS-Cog: Change from Baseline Score  
Summary Statistics in the LOCF Population**

Visit	Statistic	6-12	1-4	PBO	6-12 vs PBO	1-4 vs PBO
Week 12	N	179	217	217		
	Baseline Mean	22.91	22.72	21.15		
	Mean Change	1.02	-1.40	-2.22	0.000*	0.113
Week 18	N	179	217	217		
	Baseline Mean	22.91	22.72	21.15		
	Mean Change	0.49	-1.66	-3.34	0.000*	0.002*
Week 26	N	179	217	217		
	Baseline Mean	22.91	22.72	21.15		
	Mean Change	0.45	-2.22	-3.88	0.000*	0.004*

- Higher change scores indicate greater improvement.
- Baseline adjusted change indicated by (adj). Where adjusted changes not given, ANCOVA assumptions not met.
- \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANCOVA/ANOVA (SAS Type III analysis).
- Details of the analysis are found in the appendices.

**ADAS-Cog: Change from Baseline Score  
Summary Statistics in the OC Population**

Visit	Statistic	6-12	1-4	PBO	6-12 vs PBO	1-4 vs PBO
Week 12	N	176	216	216		
	Baseline Mean	22.86	22.75	21.19		
	Mean Change	1.05	-1.40	-2.27	0.000*	0.096
Week 18	N	158	207	201		
	Baseline Mean	23.28	22.85	20.79		
	Mean Change	0.53	-1.77	-3.45	0.000*	0.003*
Week 26	N	145	194	192		
	Baseline Mean	23.65	22.17	21.12		
	Mean Change	0.79	-2.27	-4.15	0.000*	0.002*

- Higher change scores indicate greater improvement.
- Baseline adjusted change indicated by (adj). Where adjusted changes not given, ANCOVA assumptions not met.
- \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANCOVA/ANOVA (SAS Type III analysis).
- Details of the analysis are found in the appendices.

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TABLE 36

**ADAS-Cog - Without Attention Item**  
**Mean Change From Baseline**  
**Summary P-values from Analysis of Covariance/Variance**

Variable	Visit	Treatment	Center	Treatment x Center Interaction	Pairwise Comparison P-values(+-)		
					6-12 vs PBO	1-4 vs PBO	6-12 vs 1-4
Intent-to-Treat	Week 12	0.000*	0.05*	0.026*	0.000*	0.200	0.000*
	Week 18	0.000*	0.001*	0.174	0.000*	0.002*	0.002*
	Week 26	0.000*	0.021*	0.774	0.000*	0.002*	0.000*
Last Observation Carried Forward	Week 12	0.000*	0.065	0.048*	0.000*	0.113	0.000*
	Week 18	0.000*	0.004*	0.188	0.000*	0.002*	0.000*
	Week 26	0.000*	0.008*	0.816	0.000*	0.004*	0.000*
Observed Cases (OC)	Week 12	0.000*	0.069	0.042*	0.000*	0.096	0.000*
	Week 18	0.000*	0.001*	0.254	0.000*	0.003*	0.000*
	Week 26	0.000*	0.005*	0.853	0.000*	0.002*	0.000*
OC-RDO	Week 12	0.000*	0.058	0.015*	0.000*	0.130	0.000*
	Week 18	0.000*	0.006*	0.479	0.000*	0.002*	0.002*
	Week 26	0.000*	0.026*	0.947	0.000*	0.000*	0.000*
Retrieved Drop Out (RDO) **	Week 12	0.537			0.278	0.374	0.983
	Week 18	0.216			0.086	0.455	0.488
	Week 26	0.030*			0.009*	0.093	0.733

\* Based on ANCOVA/ANOVA with treatment and center as factors  
 \*\* RDO results base on one-way ANCOVA/ANOVA

**CIBIC - Plus**  
**Mean Rating of Change from Baseline**  
**Summary P-values from Analysis of Variance**

Variable	Visit	Treatment	Center	Treatment x Center Interaction	Pairwise Comparison P-values(+-)		
					6-12 vs PBO	1-4 vs PBO	6-12 vs 1-4
Intent-to-Treat	Week 12	0.059	0.220	0.350	0.047*	0.885	0.002*
	Week 18	0.127	0.067	0.212	0.060	0.795	0.124
	Week 26	0.018*	0.007*	0.787	0.010*	0.019*	0.824
Last Observation Carried Forward	Week 12	0.010*	0.032*	0.423	0.013*	0.699	0.004*
	Week 18	0.008*	0.002*	0.064	0.005*	0.919	0.007*
	Week 26	0.008*	0.001*	0.873	0.002*	0.048*	0.250
Observed Cases (OC)	Week 12	0.010*	0.032*	0.423	0.013*	0.699	0.004*
	Week 18	0.021*	0.001*	0.036*	0.012*	0.885	0.017*
	Week 26	0.010*	0.001*	0.918	0.010*	0.009*	0.842
OC-RDO	Week 12	0.059	0.220	0.350	0.047*	0.885	0.002*
	Week 18	0.058	0.018*	0.200	0.035*	0.991	0.038*
	Week 26	0.010*	0.001*	0.852	0.009*	0.010*	0.901
Retrieved Drop Out (RDO) **	Week 12	0.846			0.565	0.721	0.918
	Week 18	0.409			0.954	0.244	0.200
	Week 26	0.440			0.269	0.952	0.371

\* Based on ANCOVA/ANOVA with treatment and center as factors  
 \*\* RDO results base on one-way ANCOVA/ANOVA

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TABLE 4

**CIBIC-Plus: Mean Rating of Change From Baseline  
Summary Statistics in the ITT Population**

Visit	Statistic	6-12	1-4	PBO	6-12 vs PBO	1-4 vs PBO
Week 12	N	209	223	219		
	Mean	4.00	4.20	4.18	0.047*	0.885
Week 18	N	214	225	223		
	Mean	4.00	4.17	4.20	0.060	0.795
Week 26	N	214	225	224		
	Mean	4.20	4.23	4.49	0.010*	0.019*

1. Lower scores indicate greater improvement.  
 2. Not Applicable  
 3. \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANOVA (SAS Type III analysis).  
 4. Details of the analysis are found in the appendices.

**CIBIC-Plus: Mean Rating of Change From Baseline  
Summary Statistics in the LOCF Population**

Visit	Statistic	6-12	1-4	PBO	6-12 vs PBO	1-4 vs PBO
Week 12	N	174	215	213		
	Mean	3.92	4.20	4.16	0.013*	0.699
Week 18	N	178	217	217		
	Mean	3.88	4.17	4.18	0.005*	0.919
Week 26	N	178	217	218		
	Mean	4.09	4.22	4.44	0.002*	0.048*

1. Lower scores indicate greater improvement.  
 2. Not Applicable  
 3. \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANOVA (SAS Type III analysis).  
 4. Details of the analysis are found in the appendices.

**CIBIC-Plus: Mean Rating of Change From Baseline  
Summary Statistics in the OC Population**

Visit	Statistic	6-12	1-4	PBO	6-12 vs PBO	1-4 vs PBO
Week 12	N	174	215	213		
	Mean	3.92	4.20	4.16	0.013*	0.699
Week 18	N	155	206	203		
	Mean	3.87	4.14	4.16	0.012*	0.885
Week 26	N	145	195	197		
	Mean	4.13	4.16	4.48	0.010*	0.009*

1. Lower scores indicate greater improvement.  
 2. Not Applicable  
 3. \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANOVA (SAS Type III analysis).  
 4. Details of the analysis are found in the appendices.

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TABLE 5

**CIBIC-Plus: Categorical Analysis: Patients with Improvement in the ITT Population**

Visit	6-12mg		1-4mg		PBO		6-12mg vs PBO	1-4mg vs PBO
	N	n (%)	N	n (%)	N	n (%)		
Week 12	209	47 (22)	223	37 (17)	219	42 (19)	0.397	0.399
Week 18	214	56 (26)	225	48 (21)	223	48 (22)	0.254	0.972
Week-26	214	47 (22)	225	50 (22)	224	34 (15)	0.068	0.046

--Improvement: CIBIC-plus 1, 2, 3  
 -Pairwise P-Values are based on Mantel-Haenszel test blocking for center  
 \* P < 0.05

As shown in Text Table 9.7.2.8, a significantly greater percentage of ENA 6-12 mg patients (24%) than placebo patients (16%) were rated improved at Week 26 in the LOCF population.

**CIBIC-Plus: Categorical Analysis: Patients with Improvement in the LOCF Population**

Visit	6-12mg		1-4mg		PBO		6-12mg vs PBO	1-4mg vs PBO
	N	n (%)	N	n (%)	N	n (%)		
Week 12	174	38 (22)	215	36 (17)	213	40 (19)	0.332	0.460
Week 18	178	51 (29)	217	47 (22)	217	47 (22)	0.055	0.934
Week 26	178	42 (24)	217	49 (23)	218	34 (16)	0.025	0.060

--Improvement: CIBIC-plus 1, 2, 3  
 -Pairwise P-Values are based on Mantel-Haenszel test blocking for center  
 \* P < 0.05

Text Table 9.7.2.9 displays the results of this analysis in the OC population. A significantly greater percentage of patients in the ENA 6-12 mg (24%) and 1-4 mg (25%) groups than the placebo (16%) group were rated improved at Week 26.

**CIBIC-Plus: Categorical Analysis: Patients with Improvement in the OC Population**

Visit	6-12mg		1-4mg		PBO		6-12mg vs PBO	1-4mg vs PBO
	N	n (%)	N	n (%)	N	n (%)		
Week 12	174	38 (22)	215	36 (17)	213	40 (19)	0.332	0.460
Week 18	155	48 (31)	206	46 (22)	203	47 (23)	0.068	0.823
Week 26	145	35 (24)	195	48 (25)	197	31 (16)	0.029	0.019

--Improvement: CIBIC-plus 1, 2, 3  
 -Pairwise P-Values are based on Mantel-Haenszel test blocking for center  
 \* P < 0.05

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## Population Summary: by Treatment

Population Grouping	6-12mg	1-4mg	PBO	Total
	N	N	N	N
Randomized (Intent-to-Treat)	243	243	239	725
Patients receiving study medication	242	242	239	723
Safety - Patients with at least one on drug safety evaluation	242	242	239	723
Last Observation Carried Forward - Efficacy	203	229	228	660
Retrieved Dropouts at Week 26 - Efficacy	36	19	17	72

Patients randomized but not receiving study medication:  
 6-12mg 35015  
 1-4mg 10011

## Patient Disposition by Treatment

Variable		6-12mg	1-4mg	PBO
Randomized	N	243	243	239
Completed	n Pct	164 (67)	209 (86)	208 (87)
Discontinued	n Pct	79 (33)	34 (14)	31 (13)
Reason for Disc:	Adverse Experiences	55 (23)	19 (7)	16 (7)
	--Adverse Events	55 (23)	18 (7)	16 (7)
	Death	1 (<1)	0	0
	Withdr. of Consent	11 (5)	5 (2)	6 (3)
	Protocol Violation	3 (1)	2 (1)	1 (<1)
	Treatment Failure	2 (1)	1 (<1)	2 (1)
	Failure Return Visits	2 (1)	3 (1)	2 (1)
	Other	5 (2)	5 (2)	4 (2)

Variable		6-12mg vs PBO	1-4mg vs PBO
Randomized	N		
Completed	n Pct		
Discontinued	n Pct	<0.001 *	0.790
Reason for Disc:	Adverse Experiences	<0.001 *	0.859
	--Adverse Events	<0.001 *	0.859
	Death	1.000	
	Withdr. of Consent	0.324	0.770
	Protocol Violation	0.623	1.000
	Treatment Failure	1.000	0.621
	Failure Return Visits	1.000	1.000
	Other	1.000	1.000

831 patients screened (3 further patients were screened for whom no data is available on the database)  
 Percentages based on number of patients randomized within each treatment group  
 Pairwise comparisons based on Fisher's Exact Test, \* p < 0.05  
 Three patients given reasons for discontinuation as "other" actually discontinued due to adverse  
 experiences (see errata, Attachment 2):  
 6-12mg: 15002 - ECG abnormality  
 1-4mg: 02016 - vital sign abnormality (bradycardia); 46004 - AE (orthostatic hypotension)

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TABLE 7

## Demography and Background Information by Treatment (ITT)

Variable	6-12mg N = 243	1-4mg N = 243	PBO N = 239	P-values
Age (years)				
N	243	243	239	0.276 *
Mean	71.3	72.3	72.4	
Std	8.30	8.09	7.87	
Median	73.0	73.0	73.0	
Min				
Max				
Age (%)				
<65	57 (23)	47 (19)	44 (18)	nd
66-75	114 (47)	107 (44)	108 (45)	
76-85	68 (28)	86 (35)	81 (34)	
>85	4 (2)	3 (1)	6 (3)	
Sex (%)				
Male	94 (39)	106 (44)	97 (41)	0.536 **
Female	149 (61)	137 (56)	142 (59)	
Height (cm)				
N	242	239	238	0.494 *
Mean	164.1	164.9	165.0	
Std	8.31	9.16	8.97	
Median	163.0	165.0	165.0	
Min				
Max				
Weight (kg)				
N	240	237	234	0.776 *
Mean	66.5	66.9	66.0	
Std	13.37	13.44	13.67	
Median	67.0	65.0	64.5	
Min				
Max				
Race (%)				
Caucasian	239 (98)	231 (95)	233 (97)	0.145 **
Black	2 (1)	5 (2)	4 (2)	
Oriental	1 (<1)	0 (0)	0 (0)	
Other	1 (<1)	7 (3)	2 (1)	
Dementia Dur (Months)				
N	242	242	239	0.889 *
Mean	38.5	39.5	39.0	
Std	23.54	23.66	24.26	
Median	36.0	36.0	36.0	
Min				
Max				

\* Based on one-way analysis of variance

\*\* Based on Chi-square test

\* p &lt; 0.05

Std=Standard Deviation Min=Minimum Max=Maximum Dur=duration nd=not done

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## ADAS-Cog: Mean Change from Baseline in the ITT Population

Visit	Statistic	6-12	1-4	PBO	6-12 vs PBO	1-4 vs PBO
Week 12	N	242	242	238		
	Baseline Mean	23.93	23.82	23.23		
	Mean Change	1.48	-0.10	0.13	0.009*	0.646
Week 18	N	242	242	238		
	Baseline Mean	23.93	23.82	23.23		
	Mean Change	0.32	-0.43	-0.94	0.023*	0.359
Week 26	N	242	242	238		
	Baseline Mean	23.93	23.82	23.23		
	Mean Change (adj)	0.26	-1.37	-1.34	0.011*	0.971

1. Higher change scores indicate greater improvement.
2. Baseline adjusted change indicated by (adj). Where adjusted changes not given, ANCOVA assumptions not met.
3. \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANCOVA/ANOVA (SAS Type III analysis).
4. Details of the analysis are found in the appendices.

## ADAS-Cog: Mean Change from Baseline in the LOCF Population

Visit	Statistic	6-12	1-4	PBO	6-12 vs PBO	1-4 vs PBO
Week 12	N	199	226	225		
	Baseline Mean	24.35	23.94	23.10		
	Mean Change	1.79	-0.10	0.08	0.003*	0.735
Week 18	N	199	226	225		
	Baseline Mean	24.35	23.94	23.10		
	Mean Change	0.69	-0.51	-1.08	0.003*	0.329
Week 26	N	199	226	225		
	Baseline Mean	24.35	23.94	23.10		
	Mean Change (adj)	0.83	-1.24	-1.45	0.001*	0.747

1. Higher change scores indicate greater improvement.
2. Baseline adjusted change indicated by (adj). Where adjusted changes not given, ANCOVA assumptions not met.
3. \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANCOVA/ANOVA (SAS Type III analysis).
4. Details of the analysis are found in the appendices.

## ADAS-Cog: Mean Change from Baseline in the OC Population

Visit	Statistic	6-12	1-4	PBO	6-12 vs PBO	1-4 vs PBO
Week 12	N	198	223	224		
	Baseline Mean	24.46	24.25	23.08		
	Mean Change	1.84	-0.15	0.08	0.002*	0.679
Week 18	N	172	213	210		
	Baseline Mean	24.61	23.84	23.02		
	Mean Change	0.89	-0.34	-1.22	0.001*	0.157
Week 26	N	157	202	205		
	Baseline Mean	23.96	24.03	22.66		
	Mean Change (adj)	1.17	-1.24	-1.41	0.001*	0.822

1. Higher change scores indicate greater improvement.
2. Baseline adjusted change indicated by (adj). Where adjusted changes not given, ANCOVA assumptions not met.
3. \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANCOVA/ANOVA (SAS Type III analysis).
4. Details of the analysis are found in the appendices.

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TABLE 8b

ADAS-Cog - Without Attention Item  
Mean Change From Baseline  
Summary P-values from Analysis of Covariance/Variance

Variable	Visit	Treatment	Center	Treatment x Center Interaction	Pairwise Comparison P-values(+)		
					6-12 vs PBO	1-4 vs PBO	6-12 vs 1-4
Intent-to-Treat	Week 12	0.004*	0.052	0.235	0.009*	0.646	0.002*
	Week 18	0.074	0.037*	0.640	0.023*	0.359	0.174
	Week 26	0.012*	0.119	0.689	0.011*	0.971	0.009*
Last Observation Carried Forward	Week 12	0.001*	0.042*	0.351	0.003*	0.735	0.001*
	Week 18	0.012*	0.022*	0.570	0.003*	0.329	0.046*
	Week 26	0.001*	0.188	0.600	0.001*	0.747	0.003*
Observed Cases (OC)	Week 12	0.001*	0.046*	0.354	0.002*	0.679	0.001*
	Week 18	0.006*	0.015*	0.604	0.001*	0.157	0.056
	Week 26	0.002*	0.197	0.731	0.001*	0.822	0.002*
OC+RDO	Week 12	0.002*	0.073	0.291	0.008*	0.476	0.001*
	Week 18	0.053	0.018*	0.721	0.015*	0.214	0.211
	Week 26	0.008*	0.059	0.749	0.009*	0.838	0.004*
Retrieved Drop Out (RDO) **	Week 12	0.697			0.661	0.962	0.439
	Week 18	0.579			0.305	0.583	0.748
	Week 26	0.428			0.674	0.247	0.285

\* Based on ANCOVA/ANOVA with treatment and center as factors  
 \*\* RDO results base on one-way ANCOVA/ANOVA  
 \* p < 0.05

CIBIC - Plus  
Mean Rating of Change from Baseline  
Summary P-values from Analysis of Variance

Variable	Visit	Treatment	Center	Treatment x Center Interaction	Pairwise Comparison P-values(+)		
					6-12 vs PBO	1-4 vs PBO	6-12 vs 1-4
Intent-to-Treat	Week 12	0.456	0.022*	0.813	0.408	0.695	0.221
	Week 18	0.201	0.140	0.745	0.088	0.698	0.183
	Week 26	0.002*	0.000*	0.408	0.000*	0.291	0.014*
Last Observation Carried Forward	Week 12	0.533	0.094	0.834	0.437	0.742	0.273
	Week 18	0.300	0.092	0.859	0.134	0.712	0.252
	Week 26	0.010*	0.000*	0.766	0.003*	0.283	0.048*
Observed Cases (OC)	Week 12	0.542	0.100	0.772	0.498	0.662	0.271
	Week 18	0.209	0.276	0.922	0.100	0.841	0.144
	Week 26	0.041*	0.000*	0.674	0.012*	0.361	0.098
OC+RDO	Week 12	0.341	0.026*	0.784	0.336	0.640	0.150
	Week 18	0.198	0.258	0.873	0.106	0.937	0.122
	Week 26	0.011*	0.000*	0.384	0.004*	0.524	0.025*
Retrieved Drop Out (RDO) **	Week 12	0.637			0.392	0.348	0.787
	Week 18	0.593			0.579	0.774	0.355
	Week 26	0.187			0.150	0.991	0.126

\* Based on ANCOVA/ANOVA with treatment and center as factors  
 \*\* RDO results base on one-way ANCOVA/ANOVA  
 \* p < 0.05

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## CIBIC-Plus: Mean Rating of Change from Baseline in the ITT population

Visit	Statistic	6-12	1-4	PBO	6-12 vs PBO	1-4 vs PBO
Week 12	N	211	228	224		
	Baseline Mean	0.00	0.00	0.00		
	Mean Change	3.89	4.04	3.99	0.408	0.695
Week 18	N	219	233	228		
	Baseline Mean	0.00	0.00	0.00		
	Mean Change	3.93	4.10	4.15	0.088	0.698
Week 26	N	219	233	230		
	Baseline Mean	0.00	0.00	0.00		
	Mean Change	3.91	4.24	4.38	0.000*	0.291

1. Lower scores indicate greater improvement.
2. Not Applicable
3. \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANOVA (SAS Type III analysis).
4. Details of the analysis are found in the appendices.

## CIBIC-Plus: Mean Rating of Change from Baseline in the LOCF population

Visit	Statistic	6-12	1-4	PBO	6-12 vs PBO	1-4 vs PBO
Week 12	N	190	220	222		
	Baseline Mean	0.00	0.00	0.00		
	Mean Change	3.88	4.01	3.97	0.437	0.742
Week 18	N	193	224	225		
	Baseline Mean	0.00	0.00	0.00		
	Mean Change	3.91	4.07	4.11	0.134	0.712
Week 26	N	193	224	226		
	Baseline Mean	0.00	0.00	0.00		
	Mean Change	3.88	4.17	4.32	0.003*	0.283

1. Lower scores indicate greater improvement.
2. Not Applicable
3. \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANOVA (SAS Type III analysis).
4. Details of the analysis are found in the appendices.

## CIBIC-Plus: Mean Rating of Change from Baseline in the OC population

Visit	Statistic	6-12	1-4	PBO	6-12 vs PBO	1-4 vs PBO
Week 12	N	190	220	222		
	Baseline Mean	0.00	0.00	0.00		
	Mean Change	3.88	4.01	3.96	0.498	0.652
Week 18	N	166	205	204		
	Baseline Mean	0.00	0.00	0.00		
	Mean Change	3.85	4.06	4.09	0.100	0.841
Week 26	N	155	198	197		
	Baseline Mean	0.00	0.00	0.00		
	Mean Change	3.93	4.20	4.34	0.012*	0.361

1. Lower scores indicate greater improvement.
2. Not Applicable
3. \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANOVA (SAS Type III analysis).
4. Details of the analysis are found in the appendices.

## CIBIC-Plus: Categorical Analysis - Patients with Improvement in the ITT population

Visit	6-12mg		1-4mg		PBO		6-12mg vs PBO	1-4mg vs PBO
	N	n (%)	N	n (%)	N	n (%)		
Week 12	211	71 (34)	228	59 (30)	224	55 (25)	0.054	0.165
Week 18	219	75 (34)	233	53 (27)	228	57 (25)	0.043 *	0.604
Week 26	219	80 (37)	233	59 (30)	230	46 (20)	<0.001 *	0.014 *

\*\*Improvement: CIBIC-plus 1, 2, 3  
 \*Pairwise P-Values are based on Mantel-Haenszel test blocking for center  
 \* P < 0.05

A significantly greater percentage of 6-12mg patients (40%) and 1-4mg patients (32%) than placebo patients (22%) were rated improved at Week 26 in the LOCF population. At Weeks 12 and 18, significantly more 6-12mg patients than placebo patients were rated improved, but there was no significant difference between the 1-4mg and placebo groups at these timepoints (Text Table 9.7.2.8).

Text Table 9.7.2.8

## CIBIC-Plus: Categorical Analysis - Patients with Improvement in the LOCF population

Visit	6-12mg		1-4mg		PBO		6-12mg vs PBO	1-4mg vs PBO
	N	n (%)	N	n (%)	N	n (%)		
Week 12	190	68 (36)	220	57 (30)	222	55 (25)	0.039 *	0.164
Week 18	193	70 (36)	224	51 (27)	225	57 (25)	0.040 *	0.607
Week 26	193	78 (40)	224	71 (32)	226	49 (22)	<0.001 *	0.010 *

\*\*Improvement: CIBIC-plus 1, 2, 3  
 \*Pairwise P-Values are based on Mantel-Haenszel test blocking for center  
 \* P < 0.05

A significantly greater percentage of patients in the 6-12mg (41%) and 1-4mg (31%) groups than in the placebo (22%) group were rated improved at Week 26 in the OC population. At Week 12, significantly more 6-12mg patients (36%) than placebo patients (25%) were rated improved (Text Table 9.7.2.9).

Text Table 9.7.2.9

## CIBIC-Plus: Categorical Analysis - Patients with Improvement in the OC population

Visit	6-12mg		1-4mg		PBO		6-12mg vs PBO	1-4mg vs PBO
	N	n (%)	N	n (%)	N	n (%)		
Week 12	190	68 (36)	220	57 (30)	222	55 (25)	0.039 *	0.164
Week 18	166	64 (39)	211	56 (27)	210	54 (26)	0.055	0.835
Week 26	155	63 (41)	198	52 (31)	197	44 (22)	<0.001 *	0.022 *

\*\*Improvement: CIBIC-plus 1, 2, 3  
 \*Pairwise P-Values are based on Mantel-Haenszel test blocking for center  
 \* P < 0.05

TABLE 11

Population Summary: By Treatment

Population Grouping	9mg	6mg	3mg	PBO	Total
	N	N	N	N	N
Randomized (Intent-to-Treat)	178	176	175	173	702
Patients receiving study medication	177	175	170	172	694
Safety - Patients with at least one on drug safety evaluation	177	175	170	172	694
Last Observation Carried Forward - Efficacy	136	142	152	161	591
Retrieved Dropouts at Week 26 - Efficacy	18	10	17	13	58

Patients randomized but not receiving study medication-  
 9mg: 13041  
 6mg: 13011  
 3mg: 02028 03066 07013 10052 13033  
 PBO: 12035

Patient Disposition: By Treatment

Variable		9mg	6mg	3mg	PBO
Randomized	N	178	176	175	173
Completed	n Pct	91 (51)	111 (63)	130 (74)	130 (75)
Discontinued	n Pct	87 (49)	65 (37)	45 (26)	43 (25)
Reason for Disc:	Adverse Experiences	60 (34)	37 (21)	17 (10)	21 (12)
	--Adverse Events	60 (34)	37 (21)	17 (10)	21 (12)
	Withdr. of Consent	16 (9)	15 (9)	12 (7)	4 (2)
	Protocol Violation	2 (1)	3 (2)	4 (2)	4 (2)
	Treatment Failure	1 (1)	0	1 (1)	0
	Failure Return Visits	5 (3)	5 (3)	3 (2)	4 (2)
	Other	3 (2)	5 (3)	9 (5)	10 (6)

Variable		9mg vs PBO	6mg vs PBO	3mg vs PBO
Randomized	N			
Completed	n Pct			
Discontinued	n Pct			
Reason for Disc:	Adverse Experiences	<0.001 *	0.015 *	0.902
	--Adverse Events	<0.001 *	0.031 *	0.496
	Withdr. of Consent	<0.001 *	0.031 *	0.496
	Protocol Violation	0.010 *	0.016 *	0.070
	Treatment Failure	0.443	0.722	1.000
	Failure Return Visits	1.000	1.000	1.000
	Other	0.050	0.197	0.637

943 patients screened  
 Percentages based on number of patients randomized within each treatment group  
 Pa. wise comparisons based on Fisher's Exact Test. \* p < 0.05

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 ON ORIGINAL

TABLE 12

**Demographic and Background Information: By Treatment  
ITT Population**

Variable	9mg N = 178	6mg N = 176	3mg N = 175	PBO N = 173	P-values
Age (years)					
N	178	176	175	173	0.299 *
Mean	74.9	73.3	73.8	74.3	
Std	8.33	8.20	9.13	7.70	
Median	76.0	74.5	76.0	75.0	
Min					
Max					
Age (%)					
<=65	25 (14)	34 (19)	31 (18)	21 (12)	
66-75	55 (31)	59 (34)	55 (31)	69 (40)	
76-85	83 (47)	77 (44)	81 (46)	77 (45)	
>85	15 (8)	6 (3)	8 (5)	6 (3)	
Sex (%)					
Male	81 (46)	73 (41)	80 (46)	74 (43)	0.819 **
Female	97 (54)	103 (59)	95 (54)	99 (57)	
Height (cm)					
N	178	176	173	173	0.897 *
Mean	165.3	164.8	165.6	165.1	
Std	9.86	10.80	10.13	10.59	
Median	165.0	165.0	165.0	165.0	
Min					
Max					
Weight (kg)					
N	175	176	175	173	0.866 *
Mean	68.9	68.5	68.7	67.7	
Std	12.56	13.91	14.34	15.76	
Median	68.0	68.0	68.0	67.0	
Min					
Max					
Race (%)					
Caucasian	156 (88)	159 (90)	149 (85)	156 (90)	0.711 **
Black	14 (8)	12 (7)	19 (11)	13 (8)	
Asian/Oriental	1 (1)	2 (1)	1 (1)	0 (0)	
Other	7 (4)	3 (2)	6 (3)	4 (2)	
Dementia Dur (Months)					
N	177	176	175	173	0.945 *
Mean	37.7	36.8	36.3	36.2	
Std	27.80	21.13	28.11	21.75	
Median	30.0	36.0	24.0	30.0	
Min					
Max					

\* Based on one-way analysis of variance  
 \*\* based on Chi-square test  
 \* P < 0.05  
 Std=Standard Deviation Min=Minimum Max=Maximum

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ON ORIGINAL**

**ADAS-Cog: Change from Baseline Score  
Summary Statistics for the ITT Population**

Visit	Statistic	9mg	6mg	3mg	PBO	9mg vs PBO	6mg vs PBO	3mg vs PBO
Week 12	N	177	176	175	171			
	Baseline Mean	22.11	21.88	21.97	21.82			
	Mean Change (adj)	-0.25	-0.44	-0.29	-0.84	0.230	0.406	0.263
Week 18	N	177	176	175	171			
	Baseline Mean	22.11	21.88	21.97	21.82			
	Mean Change	-0.73	-0.71	-0.72	-1.74	0.047*	0.044*	0.046*
Week 26	N	177	176	175	171			
	Baseline Mean	22.11	21.88	21.97	21.82			
	Mean Change	-1.15	-0.86	-1.68	-2.42	0.018*	0.004*	0.167

- Higher change scores indicate greater improvement.
- Baseline adjusted change indicated by (adj). Where adjusted changes not given, ANCOVA assumptions not met.
- \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANCOVA/ANOVA (SAS Type III analysis).
- Details of the analysis are found in the appendices.

**ADAS-Cog: Change from Baseline Score  
Summary Statistics for the LOCF Population**

Visit	Statistic	9mg	6mg	3mg	PBO	9mg vs PBO	6mg vs PBO	3mg vs PBO
Week 12	N	134	140	152	159			
	Baseline Mean	22.15	21.81	21.53	21.93			
	Mean Change (adj)	0.30	-0.50	-0.23	-0.94	0.025*	0.420	0.184
Week 18	N	134	140	152	159			
	Baseline Mean	22.15	21.81	21.53	21.93			
	Mean Change	-0.00	-0.67	-0.76	-1.93	0.001*	0.025*	0.032*
Week 26	N	134	140	152	159			
	Baseline Mean	22.15	21.81	21.53	21.93			
	Mean Change	-0.36	-0.98	-1.76	-2.54	0.000*	0.009*	0.179

- Higher change scores indicate greater improvement.
- Baseline adjusted change indicated by (adj). Where adjusted changes not given, ANCOVA assumptions not met.
- \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANCOVA/ANOVA (SAS Type III analysis).
- Details of the analysis are found in the appendices.

**ADAS-Cog: Change from Baseline Score  
Summary Statistics for the OC Population**

Visit	Statistic	9mg	6mg	3mg	PBO	9mg vs PBO	6mg vs PBO	3mg vs PBO
Week 12	N	133	140	150	158			
	Baseline Mean	22.22	21.81	21.19	21.75			
	Mean Change (adj)	0.33	-0.50	-0.22	-0.94	0.023*	0.433	0.181
Week 18	N	95	126	138	141			
	Baseline Mean	22.28	21.93	21.30	21.66			
	Mean Change	0.07	-0.83	-0.87	-1.90	0.003*	0.083	0.083
Week 26	N	87	108	123	129			
	Baseline Mean	21.70	22.13	21.00	21.66			
	Mean Change	-0.84	-1.00	-2.09	-2.61	0.017*	0.021*	0.442

- Higher change scores indicate greater improvement.
- Baseline adjusted change indicated by (adj). Where adjusted changes not given, ANCOVA assumptions not met.
- \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANCOVA/ANOVA (SAS Type III analysis).
- Details of the analysis are found in the appendices.

**ADAS-Cog - Without Attention Item**  
**Mean Change From Baseline**  
**Summary P-values from Analysis of Covariance/Variance**

Variable	Visit	Treatment	Center	Treatment x Center Interaction	Pairwise Comparison P-values(+)					
					9mg vs PBO	6mg vs PBO	3mg vs PBO	9mg vs 3mg	6mg vs 3mg	9mg vs 6mg
Intent-to-Treat	Week 12	0.616	0.228	0.344	0.230	0.406	0.263	0.937	0.770	0.709
	Week 18	0.114	0.018*	0.586	0.047*	0.044*	0.046*	0.993	0.984	0.977
	Week 26	0.021*	0.066	0.076	0.018*	0.004*	0.167	0.319	0.124	0.585
Last Observation Carried Forward	Week 12	0.153	0.337	0.384	0.025*	0.420	0.184	0.340	0.632	0.164
	Week 18	0.006*	0.129	0.651	0.001*	0.025*	0.032*	0.182	0.878	0.251
	Week 26	0.002*	0.148	0.175	0.000*	0.009*	0.179	0.020*	0.195	0.315
Observed Cases (OC)	Week 12	0.142	0.318	0.416	0.023*	0.433	0.181	0.332	0.607	0.148
	Week 18	0.030*	0.242	0.532	0.003*	0.083	0.083	0.159	0.953	0.189
	Week 26	0.037*	0.421	0.097	0.017*	0.021*	0.442	0.092	0.119	0.833
OC+RDO	Week 12	0.548	0.192	0.362	0.176	0.518	0.274	0.799	0.662	0.490
	Week 18	0.034*	0.093	0.318	0.009*	0.032*	0.027*	0.562	0.996	0.574
	Week 26	0.021*	0.421	0.094	0.019*	0.005*	0.163	0.272	0.129	0.730
Retrieved Drop Out (RDO) **	Week 12	0.804			0.405	0.947	0.739	0.713	0.782	0.439
	Week 18	0.141			0.259	0.056	0.048*	0.192	0.718	0.256
	Week 26	0.220			0.129	0.066	0.097	0.822	0.647	0.509

based on ANCOVA/ANOVA with treatment and center as factors  
RDO results base on one-way ANCOVA/ANOVA  
<0.05

**CIBIC - Plus**  
**Mean Rating of Change from Baseline**  
**Summary P-values from Analysis of Variance**

Variable	Visit	Treatment	Center	Treatment x Center Interaction	Pairwise Comparison P-values(+)					
					9mg vs PBO	6mg vs PBO	3mg vs PBO	9mg vs 3mg	6mg vs 3mg	9mg vs 6mg
Intent-to-Treat	Week 12	0.787	0.001*	0.557	0.651	0.312	0.531	0.864	0.706	0.584
	Week 18	0.803	0.028*	0.744	0.711	0.583	0.781	0.927	0.435	0.366
	Week 26	0.651	0.000*	0.311	0.244	0.862	0.836	0.343	0.975	0.331
Last Observation Carried Forward	Week 12	0.612	0.002*	0.887	0.679	0.256	0.272	0.525	0.956	0.497
	Week 18	0.650	0.021*	0.617	0.515	0.566	0.684	0.303	0.861	0.240
	Week 26	0.287	0.001*	0.341	0.084	0.688	0.974	0.094	0.714	0.197
Observed Cases (OC)	Week 12	0.612	0.002*	0.887	0.679	0.256	0.272	0.525	0.956	0.497
	Week 18	0.214	0.011*	0.216	0.123	0.912	0.574	0.041*	0.666	0.110
	Week 26	0.392	0.000*	0.531	0.150	0.537	0.869	0.116	0.444	0.422
OC+RDO	Week 12	0.787	0.001*	0.557	0.651	0.312	0.531	0.864	0.706	0.584
	Week 18	0.319	0.040*	0.435	0.116	0.994	0.949	0.103	0.945	0.128
	Week 26	0.498	0.001*	0.633	0.172	0.611	1.000	0.174	0.613	0.412
Retrieved Drop Out (RDO) **	Week 12	0.310			0.409	0.531	0.064	0.162	0.183	0.910
	Week 18	0.279			0.125	0.210	0.067	0.435	0.383	0.827
	Week 26	0.989			0.783	0.960	0.926	0.850	0.892	0.764

sed on ANCOVA/ANOVA with treatment and center as factors  
DO results base on one-way ANCOVA/ANOVA  
0.05

TABLE 14

**CIBIC-Plus: Mean Rating of Change From Baseline  
Summary Statistics for the ITT Population**

Visit	Statistic	9mg	6mg	3mg	PBO	9mg vs PBO	6mg vs PBO	3mg vs PBO
Week 12	N	158	157	157	169			
	Mean	4.00	4.06	4.02	3.95	0.651	0.312	0.531
Week 18	N	161	157	160	169			
	Mean	4.02	4.13	4.03	4.07	0.711	0.583	0.781
Week 26	N	161	157	160	169			
	Mean	4.06	4.19	4.19	4.21	0.244	0.862	0.836

1. Lower scores indicate greater improvement.
2. Not Applicable
3. \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANOVA (SAS Type III analysis).
4. Details of the analysis are found in the appendices.

**CIBIC-Plus: Mean Rating of Change From Baseline  
Summary Statistics for the LOCF Population**

Visit	Statistic	9mg	6mg	3mg	PBO	9mg vs PBO	6mg vs PBO	3mg vs PBO
Week 12	N	132	141	148	161			
	Mean	3.95	4.04	4.04	3.90	0.679	0.256	0.272
Week 18	N	133	141	151	161			
	Mean	3.94	4.10	4.08	4.03	0.515	0.566	0.684
Week 26	N	133	141	151	161			
	Mean	3.97	4.15	4.20	4.20	0.084	0.688	0.974

1. Lower scores indicate greater improvement.
2. Not Applicable
3. \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANOVA (SAS Type III analysis).
4. Details of the analysis are found in the appendices.

**CIBIC-Plus: Mean Rating of Change From Baseline  
Summary Statistics for the OC Population**

Visit	Statistic	9mg	6mg	3mg	PBO	9mg vs PBO	6mg vs PBO	3mg vs PBO
Week 12	N	132	141	148	161			
	Mean	3.95	4.04	4.04	3.90	0.679	0.256	0.272
Week 18	N	93	124	139	141			
	Mean	3.82	4.06	4.12	4.04	0.123	0.912	0.574
Week 26	N	89	104	120	129			
	Mean	3.97	4.11	4.23	4.20	0.150	0.537	0.869

1. Lower scores indicate greater improvement.
2. Not Applicable
3. \* P<0.05 (Two-Tailed). Based on pairwise t tests using pooled error term from ANOVA (SAS Type III analysis).
4. Details of the analysis are found in the appendices.

TABLE 15

**CIBIC-Plus: Categorical Analysis: Patients with Improvement in the ITT Population**

Visit	9mg		6mg		3mg		PBO		9mg vs PBO	6mg vs PBO	3mg vs PBO
	N	n (%)									
Week 12	158	44 (28)	157	38 (24)	157	46 (29)	169	49 (29)	0.817	0.303	0.974
Week 18	161	44 (27)	157	38 (24)	160	42 (26)	169	47 (28)	0.896	0.464	0.749
Week 26	161	41 (25)	157	39 (25)	160	38 (24)	169	43 (25)	0.936	0.888	0.699

\*\*Improvement: CIBIC-plus 1, 2, 3  
 \*Pairwise P-Values are based on Mantel-Haenszel test blocking for center  
 \* P < 0.05

**CIBIC-Plus: Categorical Analysis: Patients with Improvement in the LOCF Population**

Visit	9mg		6mg		3mg		PBO		9mg vs PBO	6mg vs PBO	3mg vs PBO
	N	n (%)									
Week 12	132	41 (31)	141	34 (24)	148	43 (29)	161	49 (30)	0.931	0.168	0.793
Week 18	133	41 (31)	141	34 (24)	151	39 (26)	161	46 (29)	0.578	0.410	0.618
Week 26	133	37 (28)	141	33 (23)	151	37 (25)	161	40 (25)	0.432	0.741	0.941

\*\*Improvement: CIBIC-plus 1, 2, 3  
 \*Pairwise P-Values are based on Mantel-Haenszel test blocking for center  
 \* P < 0.05

**CIBIC-Plus: Categorical Analysis: Patients with Improvement in the OC Population**

Visit	9mg		6mg		3mg		PBO		9mg vs PBO	6mg vs PBO	3mg vs PBO
	N	n (%)									
Week 12	132	41 (31)	141	34 (24)	148	43 (29)	161	49 (30)	0.931	0.168	0.793
Week 18	93	35 (38)	124	31 (25)	139	36 (26)	141	41 (29)	0.100	0.575	0.607
Week 26	89	27 (30)	104	27 (26)	120	31 (26)	129	31 (24)	0.311	0.681	0.917

\*\*Improvement: CIBIC-plus 1, 2, 3  
 \*Pairwise P-Values are based on Mantel-Haenszel test blocking for center  
 \* P < 0.05

**Review of Clinical Data/Amendment to the NDA  
Mortality in the Exelon NDA**

**NDA:** 20-823

**Sponsor:** Novartis

**Drug:** Rivastigmine

**Route of Administration:** Oral

**Reviewer:** Greg Burkhardt, M.D., M.S.

**Submission Date:** 3/9/98

**Review Completion Date:** 3/12/98

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Novartis submitted an amendment to the rivastigmine NDA on March 9, 1998. It consisted of a single volume and supporting datasets purportedly showing that all-cause mortality rates did not increase by dose with the addition of extended follow-up and 6 deaths that had misclassified in the 120 day safety update database. These 6 deaths had been classified as occurring after 30 days of last use of the drug when in fact, they were within 30 days.

In the initial review, I found two significant errors that precluded further review of the amendment or its supporting data. These are summarized below along with two relatively minor problems.

- (1) In the amendment, Novartis states that there were 3162 patients contributing 2473 person-years in the extended database. However, in the demography and drug-dose files, there were 3349 and 3350 separate PID numbers, respectively. In the person-time file that was used by Novartis to analyze the rates, there were about 2880 person-years.
- (2) Novartis provided only a limited description of the methods used to compute each patient's person-time. On page 5, there is a unclear statement in the text that notes using the entry date of the patient and in Table 1 on page 7, information is provided about the dates for each database. Because the methodology was unclear, I discussed it with the Novartis team in a teleconference on 3/11/97. As it turns out, the purported censoring date of June 30, 1997 that is listed in the table and previously interpreted by Dr. Racoosin and myself as a censoring date, is just the latest date that a death could have been included in the updates. Thus, deaths

occurring before June 30, 1997 may still have been excluded from the study. As explained to me by Novartis, if patients entered study before 1/1/96, they could have contributed up through 104 weeks of experience but not more. Any additional experience was to be censored. Thus, the censoring date was patient specific being tied to the entry date. With this explanation in mind I reviewed the supporting files and found numerous patients in the drug-dose file, which was apparently used to calculate person-time, who started before 1/1/96 (examples 30303001 and 30317001) and had more than 2 years of experience counted. Thus, I was unable to determine the methods used by Novartis to compute the person-time.

- (3) The supporting data did not include the patient visit file which we had asked for in an earlier request. This file might have been helpful in clarifying how person-time was computed.
- (4) Cases were not included in the person-time file (relatively minor since I could add them in with some work).

IS/ —  
3/12/98

Greg Burkhart, M.D., M.S.  
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cc:HFD-120\Burkhart\Leber\Oliva\Levin\Racoosin

**APPEARS THIS WAY  
ON ORIGINAL**